INVESTMENT FOR HUMANITY

1993

A Strategic Vision

for the

National Institutes of Health

A Guide to Contents

Investment for Humanity

". . . to intervene, even briefly, between our fellow creatures and their suffering or death, is our most authentic answer to the question of our humanity."

— *Howard Sackler, American playwright*

The National Institutes of Health (NIH) was established more than a century ago to improve and safeguard the health of every American. Today, NIH continues to pursue science for the sake of each man, woman, and child in the United States, reflecting the central tenet of our democratic society: the belief in the value and sanctity of the individual. Science for the sake of the citizen is an idea that has grown up with America. Thus, it is no accident that the United States, the world's greatest democracy, has created the world's greatest biomedical research establishment, dedicated to serving not the state, but the individuals who make up the state.

The fruits of NIH's medical research have proven to be among our Nation's greatest achievements, saving countless lives and profoundly improving the human condition. NIH has translated the American public's investment into far-reaching biomedical discoveries and a wealth of scientific knowledge that benefit all of humanity.

NIH is a large, complex organization. It is, in fact, a nationwide republic of science, composed of some 50,000 individual researchers working at 1,700 institutions across the country. NIH's intellectual capital base and scientific resources are devoted to addressing the most challenging, urgent public health and biomedical questions of our time. The growing complexity of these challenges — ranging from reducing the suffering from heart disease and cancer to finding a cure for AIDS — coupled with the

urgent need to manage prudently the U.S. taxpayers' $10 billion investment in NIH, requires that we think very carefully about our future.

That is precisely what occurred as we embarked upon our strategic planning effort. The leadership of NIH along with some 2,000 representatives of the scientific community — from our intramural community and from NIH-supported institutions nationwide — participated in this process. The plan is a vision, not a blueprint; it is a framework, not a manual of operations; it is a beginning, not an end. It defines an NIH flexible enough to respond to society's changing health care needs and dynamic enough to open ever more promising frontiers of fundamental research. Although a new undertaking for NIH, the Strategic Plan does not sever ties with the past. Rather, it builds on past accomplishments, organizational strengths, and approaches of proven value. This document also affirms our commitment to the individuals who are the NIH: they are the source of our creative advances, primarily through their insights, initiatives, and individual talent.

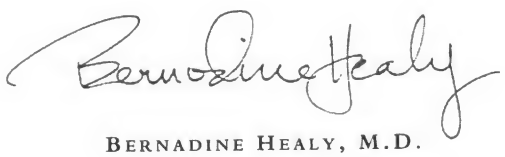
Investment for Humanity is predicated upon the need to create an environment that promotes creativity on the part of individual scientists. The pursuit of research opportunities that are closely aligned with our Nation's health goals and our citizens' individual needs is also central to our plan. By focusing NIH's organizational thinking, the Strategic Plan articulates how our community defines its priorities for investment.

The Strategic Plan starts with our statement of mission — *science in pursuit of knowledge to improve human health*. All that follows derives from and relates to that central guiding mission. Woven throughout this plan is a firm recognition of 1) a commitment to basic and clinical research as the means of expanding our knowledge base; 2) the importance of nurturing and sustaining a robust and varied human capital base; and 3) the need for sophisticated infrastructure to accomplish both. Although the specific initiatives may change as science and the needs of society change, NIH's fundamental mission and purpose will remain immutable.

There are no greater perils to our people and the promise of our Nation than the scourges of cancer, heart disease, drug and alcohol abuse, mental illness, debilitating diseases of the elderly, and new emerging threats such as AIDS and drug-resistant tuberculosis. Investing in NIH is the single greatest action our Nation can take to overcome these and other devastating illnesses. Indeed, the history of NIH and its record of achievement provide compelling evidence that no other public investment has yielded a greater return, over a longer period of time, for every U.S. citizen.

The benefits of that investment extend also to our Nation's economy. The biotechnology, bioengineering, and pharmaceutical industries (and related life-science-based corporations) are increasingly important to improving the Nation's economy — creating new jobs, technologies, products, and services. In many regions of the country, biomedical science is a great catalyst for the creation of skilled, high-level jobs and is responsible for considerable economic productivity. NIH is the engine that drives this emerging "bioeconomy": an economy that will lead to better health, lower health care costs, and sustained economic growth. The NIH Strategic Plan will help ensure that our Nation remains at the forefront of this burgeoning economy.

Investment for Humanity pledges the NIH community to address the opportunities, challenges, and needs of the future with vigor, dedication, and integrity. In turn, it also calls for a reciprocal commitment from this Nation's citizens and their elected representatives, not only to sustain, but also to enhance the strength and vitality of this unique institution — this republic of science — they have created and nurtured over many years. For NIH to fulfill its mission of pursuing science for the sake of each citizen, our vital enterprise must be a national priority.



Bernadine Healy, M.D.

Director,

National Institutes of Health

Mission and Goals

The Mission of the National Institutes of Health:

Science in pursuit of knowledge to improve human health.

This means pursuing science to expand fundamental knowledge about the nature and behavior of living systems; to apply that knowledge to extend the health of human lives; and to reduce the burdens resulting from disease and disability. The National Institutes of Health seeks to accomplish its mission by:

- Fostering fundamental discoveries, innovative research, and their applications in order to advance the Nation's capacity to protect and improve health;

- Developing, maintaining, and renewing the human and physical resources that are vital to ensure the Nation's capability to prevent disease, improve health, and enhance quality of life;

- Expanding the knowledge base in biomedical[1] and associated sciences in order to enhance America's economic well-being and ensure a continued high return on the public investment in research; and

- Exemplifying and promoting the highest level of scientific integrity, public accountability, and social responsibility in the conduct of science.

[1]The word *biomedical* is used in this document as a generic term encompassing physics, chemistry, biology, and mathematics as well as certain engineering fields and health-related sciences, including the behavioral and social sciences.

Philosophy

Preamble

The National Institutes of Health (NIH) is the steward of biomedical research for the United States. Ultimately, our success as an institution will be measured by our ability to demonstrate that the health of the public has been improved by the efforts of the scientific community we have fostered and supported.

NIH will identify and diligently pursue scientific opportunities that promise to yield fundamental, innovative, and valuable contributions to the improvement of human health. We must be poised to recognize that science is inherently mutable and unpredictable. New, expanded, and broad-based opportunities in the life sciences must be explored to find solutions to health problems and needs that will benefit our diverse population. NIH therefore makes the following commitments:

To the American Public

NIH exists to serve the people and, indeed, addressing their health needs is the essence of our mission. Our effectiveness depends on our ability to communicate and implement new knowledge expeditiously, so that advances are rapidly applied in the practices and technologies of the health sciences. We will not overpromise, but the goals we set for the health of the Nation must be of the highest order. We will endeavor to promote equity and fairness as we strive to hold and strengthen the trust and confidence of all the American people.

To Our Scientists and Employees

NIH must foster an environment in our intramural and extramural communities that ensures reasonable stability at an individual level and flexibility in the pursuit of knowledge; attends tirelessly to the support and renewal of talent, regardless of race, gender, creed, or physical disability; and fosters the values of trust, integrity, intellectual generosity and openness, propriety in collaborative endeavors, and a spirited yet measured sense of competition.

To Our Nation's Youth

NIH seeks to attract the youth of the Nation to science and scientific careers. The new ideas and innovations of tomorrow depend upon the young minds of today. Our human resource base must be nurtured now so that the remarkable advances occurring today will produce the highest possible yield in future years.

To Our Communities

NIH, which directly or indirectly employs some 100,000 people, recognizes its responsibility to local communities and the need to work effectively with local and state officials. In communities across the country, our investment forms an important funding base, source of employment, academic enhancement, and means for enrichment of the quality of regional medical care.

To Our Extramural Research and Education Institutions

NIH's long-standing ties to the scientific community reflect the productive collaborations that characterize many of today's advances in science. The educational and research institutions that comprise the scientific community form a vital part of the NIH mission. The scientific talent base and physical infrastructure nurtured by NIH are a national resource vital to the quest for scientific knowledge. These partnerships drive the entire research enterprise.

To the Federal Stewards

NIH must assure congressional leaders and executive branch officials that we are investing public resources wisely and responsibly, and that we are providing a strong return on the public's investment in NIH. With equal resolve, we must demonstrate our sensitivity to the social, legal, ethical, and economic concerns of our Federal leaders and remain responsive to their oversight responsibilities.

To Our Nation's Economy

NIH-supported biomedical research creates new products, new jobs, and new industries. The biotechnology, pharmaceutical, and medical device industries, which in large part stem from NIH-supported research, have been and will continue to be major forces in advancing our Nation's economic growth and productivity. NIH discoveries and their applications have a positive impact on one of the Nation's most intractable social and economic problems — containing and reducing health care costs. The ultimate approach to spiralling health care costs must be to prevent and cure disease.

To the International Community

NIH is committed to fostering cooperation with scientists and institutions in other nations in order to expand biomedical knowledge and create new medical products and technologies. Since its founding in 1887, NIH has forged partnerships with leading research institutions throughout the world. Intellectual exchange among biomedical scientists — like the diseases they seek to cure — cannot be confined within national boundaries.

Statement of Means

The path of scientific discovery cannot be defined in advance. NIH's leadership believes, however, that success in pursuit of our mission can be catalyzed and accelerated by judicious planning. In the face of change, promising areas of research opportunity and important issues of science policy must be identified and advanced in the interest of achieving NIH's long-term goals. This strategic planning process assures the balance and diversity of the NIH portfolio that are critical to progress. This plan outlines the strategic mechanisms for achieving the mission and goals of NIH.

NIH Corporate Role

Ultimate responsibility for fulfilling NIH's mission and goals rests with the Office of the Director and the leadership of the Institutes, Centers, and Divisions.[2] At the corporate level, responsiveness to the objectives of the Strategic Plan must be reflected in the development of coordinated strategies and the annual budget, while program initiatives and project funding decisions are to be made by the individual institutes. Oversight must be conducted broadly and must reflect the mutability and unpredictability of science.

Institute, Center, and Division Roles

The institutes provide the structure for achieving the mission and goals of NIH. Although each has a mandate with defined priorities that address science and health matters from a specific perspective, collectively they are the agents for implementing the Strategic Plan. The institutes, working with the Office of the Director, will be responsible for implementing specific initiatives that are relevant to their individual research missions.

Scientific Advisory Role

The participatory role of extramural scientists in charting the present and future course of NIH is a major strength of its corporate culture. Through the Advisory Committee to the Director, the National Advisory Councils and Boards, and the Program Advisory Committees, NIH responds to the dynamic and unpredictable nature of science. Advisory groups help us to identify the anticipated health needs and the unexpected discoveries and opportunities that can have profound consequences for the course of scientific progress. The advice that comes from NIH's peer review system is pivotal in translating scientific direction into meritorious endeavors. Indeed, the evaluation of research proposals through peer review is among the most important means whereby NIH achieves its goals and objectives.

Commitment to Science Opportunities and Health Needs

Science opportunities and the health needs of the public will drive the development of the NIH budget and the allocation of resources. In developing our future budgets, we will emphasize science and programs; mechanisms (including the number of grants) will be the important means to achieving scientific goals and programs.

[2]The word *institutes* is used in this document to refer collectively to the NIH Institutes, Centers, and Divisions.

Commitment to Scientifically Meritorious Investigator-Initiated Research

We reaffirm the principle of high-quality, investigator-initiated research as essential to discovery. Indeed, a hallmark of NIH since the 1940s has been its emphasis on the freedom of individuals to pursue their own diverse ideas within the scope of clearly defined targets. This strategy has been successful in encouraging creativity and maintaining scientific freedom, while fostering high-quality research in pursuit of NIH's mission. Investigator-initiated research is at the heart of scientific inquiry, in which discoveries arise in unexpected places, from improbable insights, and through leaps of imagination. The implementation of the NIH Strategic Plan will rely on this commitment and will continue to generate innovative approaches to support investigator-initiated research.

Commitment to the Principles of Responsible Cost Management

Responsible cost management is essential for achieving many of NIH's goals, including stability and predictability in the funding levels of biomedical research, wise and effective management of research costs, and public accountability. The concept of cost management is central to the Strategic Plan, recognizing the need for continual reexamination and evaluation. Abiding by the well-articulated principles of the cost management plan is essential to ensuring prudent and efficient stewardship of all NIH programs.

Legacy of Discovery

The National Institutes of Health (NIH) began more than a century ago as the Hygienic Laboratory, a one-room operation in the attic of the Staten Island Marine Hospital with $300 in funding and one physician. Today it is the largest, most productive biomedical research enterprise in the world, with an operating budget of more than $10 billion supporting more than 50,000 prominent investigators nationwide. NIH is the foundation of our Nation's investment in biomedical research and is the source of discoveries that have improved the health and well-being of millions of Americans. The following pages highlight some of the many accomplishments of NIH over the past century.

Attacking Infectious Diseases

From its earliest days, NIH has pioneered important advances in public health. Dr. Joseph Kinyoun, who founded the Hygienic Laboratory in 1887, made the first laboratory diagnosis in the western hemisphere of cholera, a disease that ravaged U.S. cities at that time. In 1906, research on anaphylaxis — allergic reactions to foreign proteins in the body — contributed to the study of immunology as we know it today. And it was a Hygienic Laboratory doctor who determined that pellagra was not an infectious disease, but a vitamin deficiency.

Disease Prevention

During World War I, the Hygienic Laboratory turned its attention to problems confronting the military. Significant advances in disease prevention came from research to find new ways to administer smallpox vaccinations to soldiers and to identify the carriers of tetanus and anthrax, which were infecting many soldiers.

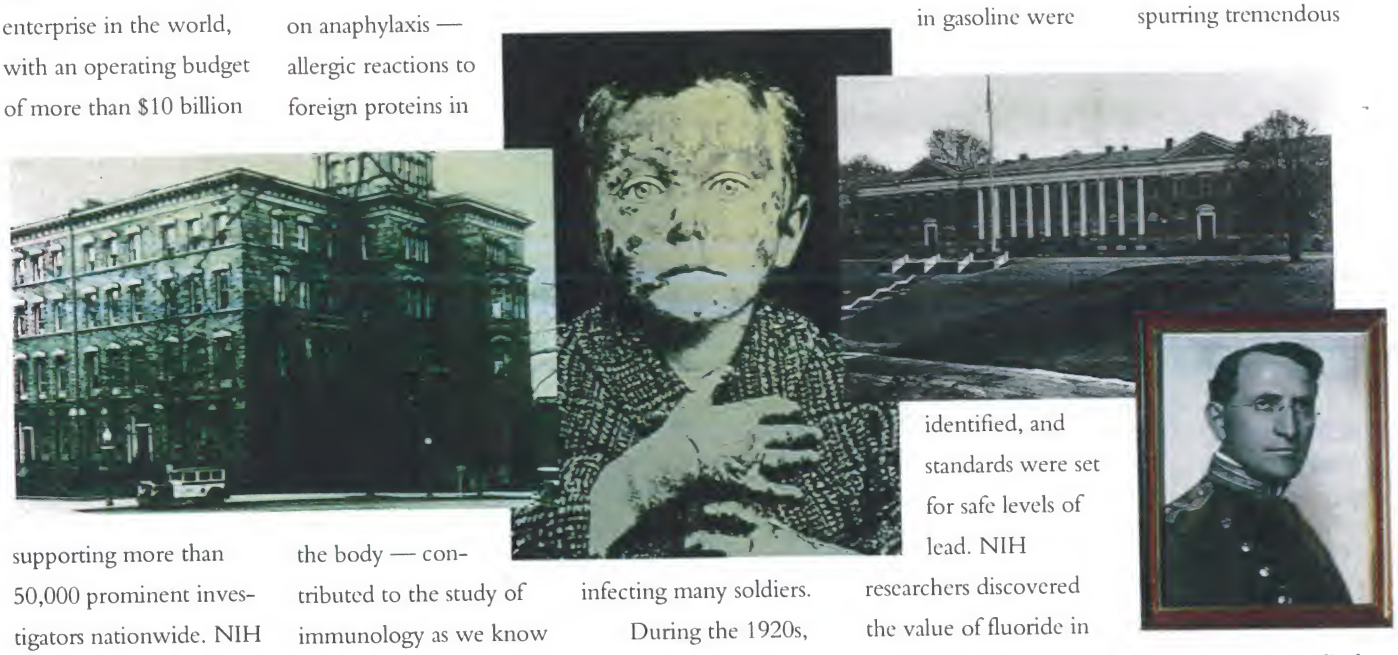
During the 1920s, expanded cooperation between the Hygienic Laboratory and the states forged new and important partnerships. Cooperation with the State of Montana led to a vaccine for Rocky Mountain spotted fever. The Rocky Mountain Laboratory, which first produced the vaccine for that disease, remains a part of NIH.

Promoting Good Health

Numerous discoveries resulting from fundamental research have had direct implications for everyday life, not just for the treatment of illness. In the late 1920s, for example, milk began to be pasteurized to prevent undulant fever, a painful, persistent disease carried by domestic animals. The dangers of tetraethyl lead in gasoline were identified, and standards were set for safe levels of lead. NIH researchers discovered the value of fluoride in preventing dental caries; this led to the determination of optimal fluoridation levels for community water systems.

NIH's Growth Spurt

Congress officially renamed the Hygienic Laboratory the National Institute of Health in 1930, and in 1937 established the National Cancer Institute (NCI), which was authorized to fund research and scientific training at universities and medical facilities, setting a precedent for Federal funding and spurring tremendous growth in biomedical research. This "extramural" program was so successful that it became an integral part of each successive institute and helped NIH expand from a small group of distinguished investigators into a national resource for medical research funding.



Today, support for investigators at institutions nationwide accounts for as much as 90 percent of the research funded by NIH.

The years following World War II witnessed a dramatic increase in Federal support for biomedical research, opening up critical areas of health and disease for NIH study. New Institutes, Centers, and

Divisions were added, and NIH's name became plural — the National Institutes of Health.

Accelerating the War Against Cancer

The 1950s and 1960s brought a number of advances in the battle against cancer when NIH scientists produced studies linking smoking and lung cancer and developed the first chemotherapy treatments to cure choriocarcinoma (a cancer of the placenta) and childhood leukemia. Today, chemotherapy is a standard cancer treatment, and the overall survival rate for cancer stands at over 50 percent, with more and more forms becoming curable.

Making Blood Transfusions Safer

One of the earliest processes to make blood transfusions safe came in the 1960s as a result of the work of an NIH-supported Nobel Prize-winning scientist. Dr. Baruch Blumberg identified a marker for the presence of hepatitis B in blood, which led to the development of technologies to screen donated blood prior to transfusion and to create a vaccine for the disease.

Cracking the Genetic Code

While working at NIH in the 1960s, Nobel Prize-winner Marshall Nirenberg deciphered the genetic code, the molecular instructions in genes that direct all life processes. This discovery set the stage for contemporary research on gene mapping, gene therapy, and molecular structure. Identifying the genes responsible for specific diseases enables scientists to search for revolutionary approaches to treat, prevent, and cure them.

Heart Disease Initiatives

Major initiatives in diagnosis, treatment, and prevention of myocardial infarction and sudden death were inaugurated at NIH in the 1970s. Since then we have seen a dramatic reduction in death and disability from coronary disease and stroke. NIH-sponsored public education programs, particularly the high blood pressure program, have played a major role in decreasing the incidence of stroke.

New Technologies

NIH's contributions in the development of positron emission tomography (PET) advanced our understanding of the function of the human brain and the biological aspects of neurological and mental disorders, including brain tumors, manic depressive illness, and schizophrenia. Soft tissues of the body can be studied noninvasively because of NIH's contributions to magnetic resonance imaging (MRI), which is providing a window on the structure and function of the brain.

Laser technology began moving to the forefront of medicine through trials supported by NIH in the 1970s, when lasers were used to seal off leaking blood vessels on the retina, thereby reducing blindness by 90 percent among diabetics. Other techniques have since been developed using lasers to treat a wide range of medical problems, such as cancer, kidney stones, and endometriosis (aberrant tissue in the pelvic cavity).

Molecular Medicine and Biotechnology

As NIH's contributions to biomedical knowledge have grown, far more attention has been focused on the cell and the processes of life at the molecular level. Almost every institute today includes some aspect of molecular medicine in its research portfolio.

Growing evidence of the genetic basis of many human diseases has led to the first human gene therapy trials being conducted at NIH on an immunologic disorder and cancer.

From its beginnings, NIH has supported research that explores basic life processes. This investment has paid off consistently with unexpected discoveries that move scientists to new frontiers in health science research, and much closer to the cures for a wide spectrum of inherited and acquired diseases. The success of this basic research has been confirmed by the world community. Since the 1950s, one or more NIH-supported scientists have been awarded the Nobel Prize almost every year.

Neuroscience and the Brain

NIH scientists have made significant advances in comprehending the function of the brain, the organ that defines our distinctively human character. They have learned much about how the billions of individual nerve cells in the brain communicate with their neighbors, how networks of cells perform specific functions, and how chemicals called neurotransmitters control the interactions among cells and networks. Other NIH researchers have discovered the role of genes in determining the structure and function of neurotransmitters, factors that influence the development of the fetal brain, how the brain develops after birth, and how it responds to injury.

These discoveries have led to progress in understanding the ways in which the brain can be injured by disease or trauma and the role of genetics in neurological disorders such as Alzheimer's or Huntington's disease. Building on this new knowledge, and using many of the same research tools, NIH scientists are finally beginning to understand that complex disorders such as depression, schizophrenia, alcoholism, and drug abuse are determined by both genetic factors and the environment — an understanding that may soon lead to the development of new therapies for both neurological and behavioral disorders.

Responding to New Disease Challenges

NIH-supported scientists are leading the world in research on HIV and AIDS. Researchers at NIH helped to establish the link between the human immunodeficiency virus and AIDS and, more importantly, developed a blood test for the virus to safeguard the world's blood supply. NIH investigators identified the first promising therapy for patients with AIDS and continue to develop new therapies that may be even more effective in the fight against this disease. AIDS research also pays dividends in other fields, including virology, immunology, microbiology, and molecular biology.

NIH research has also resulted in better understanding of the immune system, new approaches to vaccine development, novel diagnostic techniques, and new methods for evaluating drug treatments. Researchers at NIH are using computers to help explain the structure of proteins, enzymes, and DNA, and how drugs act on the body. NIH supported scientists have also made progress in the assessment of Alzheimer's disease and are exploring vaccines for many forms of cancer and other diseases. On other fronts, NIH-supported scientists are studying the part that nutrition might play in diseases such as cancer, diabetes, and osteoporosis.

In the past 40 years, we have learned more about health and disease than during any other time in history. Yet the Nation's health continues to be challenged by unforeseen threats, such as the emerging threat of multiple-drug-resistant tuberculosis. Because of the National Institutes of Health, this Nation has the intellectual and physical resources to continue to respond to such challenges to improve human health.

NIH's Nobel Laureates

Evidence that NIH is achieving its mission — science in pursuit of knowledge to improve human health — is the list of 81 recipients of science's highest honor, the Nobel Prize. Four were NIH intramural scientists at the time they received the Nobel Prize. The other laureates listed received extramural grants from NIH prior to being awarded the Nobel Prize.

1939 E. O. Lawrence (USA) *Physics*

1950 Philip S. Hench (USA) *Chemistry*; shared with E.C. Kendall and T. Reichstein

1953 Fritz A. Lipmann (USA) *Physiology or Medicine*; shared with H. A. Krebs

1954 Thomas H. Weller (USA) *Physiology or Medicine*; shared with J. F. Enders and F.C. Robbins

1954 Linus C. Pauling (USA) *Chemistry*

1955 Vincent du Vigneaud (USA) *Chemistry*

1956 Dickinson W. Richards, Jr. (USA) *Physiology or Medicine*; shared with A.Cournand and W. Forssmann

1958 George W. Beadle (USA), Joshua Lederberg (USA), and Edward L. Tatum (USA) *Physiology or Medicine*

1959 Arthur Kornberg (USA) and Severo Ochoa (USA) *Physiology or Medicine*

1960 Peter B. Medawar (United Kingdom) *Physiology or Medicine*; shared with F.M. Burnet

1962 James D. Watson (USA) *Physiology or Medicine*; shared with F.H.C. Crick and M.H.F. Wilkins

1962 John Kendrew (USA) *Chemistry*; shared with M.F. Perutz

1964 Konrad Bloch (USA) *Physiology or Medicine*; shared with F. Lynen

1965 Jacques L. Monod (France) *Physiology or Medicine*; shared with F. Jacob and A. Lwoff

1965 Robert B. Woodward (USA) *Chemistry*

1966 Charles B. Huggins (USA) *Physiology or Medicine*; shared with P. Rous

1967 Haldan K. Hartline (USA) and George Wald (USA) *Physiology or Medicine*; shared with R. Granit

1968 **Marshall W. Nirenberg*** (USA), Robert Holley (USA), and H. Gobind Khorana (USA) *Physiology or Medicine*

1968 Lars Onsager (USA) *Chemistry*

1969 Max DelbrÅck (USA), Alfred D. Hershey (USA), and Salvador Luria (USA) *Physiology or Medicine*

1970 **Julius Axelrod*** (USA) and Ulf von Euler (Sweden) *Physiology or Medicine*; shared with B. Katz

1970 Luis Leloir (Argentina) *Chemistry*

1971 Earl W. Sutherland, Jr. (USA) *Physiology or Medicine*

1972 **Christian B. Anfinsen*** (USA), Stanford Moore (USA), and William H. Stein (USA) *Chemistry*

1972 Gerald M. Edelman (USA) and Rodney R.Porter (United Kingdom) *Physiology or Medicine*

1974 Albert Claude (Belgium), Christian de Duve (Belgium), and George E. Palade (USA) *Physiology or Medicine*

1975 David Baltimore (USA), Renato Dulbecco (USA), and Howard M. Temin (USA) *Physiology or Medicine*

1976 **D. Carleton Gajdusek*** (USA) and Baruch S. Blumberg (USA) *Physiology or Medicine*

1976 William N. Lipscomb (USA) *Chemistry*

1977 Roger C.L. Guillemin (USA) and Andrew V. Schally (USA) *Physiology or Medicine*; shared with R.S. Yalow

1978 Daniel Nathans (USA) and Hamilton O. Smith (USA) *Physiology or Medicine*; shared with W. Arber

1979 Herbert Brown (USA) *Chemistry*; shared with G. Wittig

1980 Baruj Benacerraf (USA), Jean Dausset (France), and George D. Snell (USA) *Physiology or Medicine*

1980 Paul Berg (USA) and Walter Gilbert (USA) *Chemistry*; shared with F. Sanger

1981 Roald Hoffmann (USA) *Chemistry*; shared with K. Fukui

1981 David H. Hubel (USA), R.W. Sperry (USA), and Torsten N. Wiesel (USA/Sweden) *Physiology or Medicine*

1982 Sune Bergstrîm (Sweden) and John R. Vane (United Kingdom) *Physiology or Medicine*; shared with B. Samuelsson

1982 Aaron Klug (United Kingdom) *Chemistry*

1983 Henry Taube (USA) *Chemistry*

1984 R. Bruce Merrifield (USA) *Chemistry*

1985 Herbert A. Hauptman (USA) *Chemistry*; with J. Karle

1985 Michael S. Brown (USA) and Joseph L. Goldstein (USA) *Physiology or Medicine*

1986 Susumu Tonegawa (Japan/USA) *Physiology or Medicine*

1986 Stanley Cohen (USA) and Rita Levi-Montalcini (USA/Italy) *Physiology or Medicine*

1987 Donald J. Cram (USA) *Chemistry*; shared with J.-M. Lehn and C.J. Pedersen

1989 Sidney Altman (USA) and Thomas Cech (USA) *Chemistry*

1989 J. Michael Bishop (USA) and Harold E. Varmus (USA) *Physiology or Medicine*

1990 Elias J. Corey (USA) *Chemistry*

1990 E. Donnall Thomas (USA) and Joseph E.Murray (USA) *Physiology or Medicine*

1992 Edmond H. Fischer (Switzerland-USA) and Edwin G.Krebs (USA) *Physiology or Medicine*

1992 Gary Becker (USA) *Economics*

*** Current or former NIH intramural scientists.**

Trans-NIH Objectives

Objective 1 — Critical Science and Technology

Assure that critical science and technology in basic biology, with impacts on human health and the national economy, are advanced as priorities across the Nation's biomedical research enterprise.

- Molecular Medicine
- Biotechnology and Bioengineering
- Immunology and Vaccines
- Structural Biology
- Cellular and Integrative Biology

Objective 2 — Critical Health Needs

Strengthen the ability of the Nation's biomedical research enterprise to respond to current and emerging public health needs.

- Basic Biology Related to the Environment
- Behavior and Health
- Childhood Health and Mortality
- Reproductive Biology
- Disease Control and Prevention
- Bionutrition: Strengthening the Science Base
- Chronic and Recurrent Illness, Rehabilitation, and Aging
- Health of Women
- Health of Minorities and Underserved Populations

Objective 3 — Intellectual Capital

Provide for the renewal and growth of the intellectual capital base essential to the Nation's biomedical research enterprise. Ensuring fairness and equality of opportunity is central to efforts to enhance the human resource base of biomedical research.

- Development of Scientific Talent Base
- Life Sciences Education and Public Understanding of Science
- Professional Standards of Scientific Research

Objective 4 — Research Capacity

Sustain and renew the capacity that is critical to advancing the Nation's ability to conduct health-related research

- Intramural NIH: Revitalizing A National Resource
- Clinical Research
- Research Resources, Facilities, and Instrumentation

Objective 5 — Stewardship of Public Resources

Secure the maximal return on the public investment in biomedical research.

- Economic Analysis and Budget Policy
- Technology Transfer
- NIH Leadership Base
- Cost Management
- Peer Review

Objective 6 — Public Trust

Earn continually the public's respect, trust, and confidence as we carry out our mission.

- Social, Legal, Ethical, and Economic Issues in Biomedical Research
- NIH and the Nation's Economy
- Communicating with the Public

Critical Science and Technology

The quick harvest of pure science is the usable process, the manufacture, the machine.

The shy fruit of pure science is understanding.

—Lincoln Barnett, *Universe and Dr. Einstein*

By "critical science and technology" we mean the fundamental, basic research and widely applicable technologies that provide crucial underpinnings across the institutes in a range of disciplines. Opening revolutionary directions, they are essential to the success of the entire NIH enterprise, providing a base of fundamental knowledge. Investment in fundamental knowledge sets the stage for future advancements that will improve human health, reduce health care costs, and bolster the Nation's economic well-being. Evolving and dynamic, this knowledge base transcends categorical NIH missions, but is central to each of them through its contribution to the understanding of disease.

The application of such fundamental science to health and disease holds the promise of cost savings in health care, particularly for chronic and debilitating diseases. Today, and even more so in the next five to ten years, fundamental science will contribute substantially to the enhancement of the Nation's economic growth, productivity, and competitiveness, as well as our quality of life. Investment in critical science and technology is an investment in the future.

Critical science and technology forms the core activity of each of our 22 institutes and centers. All perform and support these fundamental sciences as part of their individual missions. Those institutes and centers, and each of their mostly disease-oriented missions, are outlined under Objective 2. Every institute and center has a role and a stake in the advancement of Critical Science and Technology.

Molecular Medicine

In the last two decades, scientists have greatly expanded our fundamental understanding of the molecular basis of human disease. Molecular medicine, the study of how the structure and activity of living cells are controlled by molecules such as DNA and proteins, has enabled investigators to explore and pinpoint the molecular dynamics of genetic diseases. It has also allowed them to characterize the interactive biological chain of events linked to cancer, diabetes, and other diseases. Increased knowledge of the molecular foundations of disease has led to new clinical techniques to diagnose, treat, and prevent these and other devastating illnesses. Moreover, molecular research holds great promise for reducing the social and economic impacts of a wide range of disorders. Molecular medicine is a high priority for the National Institutes of Health. This discipline is critical to the conduct of basic science and clinical research, and to the creation of new clinical therapies of benefit to patients. NIH will support molecular research to

- Map the human genome to further biomedical science's ability to identify the specific location and behavior of genes linked to inherited and acquired diseases.
- Understand both healthy and disruptive molecular activity within the human cell in order to develop tools for disease detection and intervention.
- Define the multiple biological steps and interactions — cellular and environmental — responsible for such conditions as cancer, immunodeficiency, cardiovascular and pulmonary diseases, mental illnesses, and neurodegenerative diseases.

Among our highest priorities are the following:

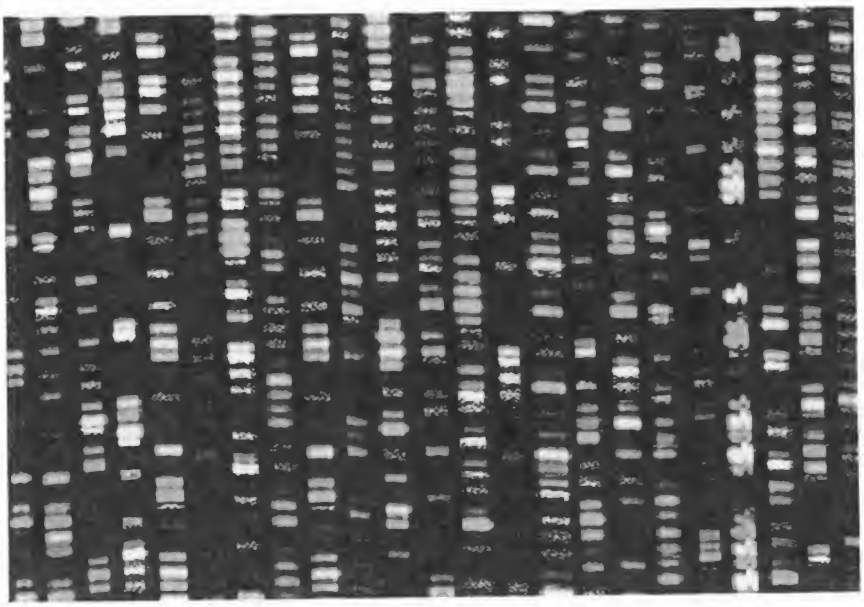
- *Human Genome Project*
- *Understanding the Molecular Basis of Disease*
- *Human Gene Therapy*

Human Genome Project

The *Human Genome Project* is a worldwide research effort to identify and map the exact location of each one of the estimated 100,000 genes in the human cell, a task of incredible complexity and magnitude. Paralleling this effort, scientists will study the DNA of model organisms to obtain clues to the organization and function of the human genome, our genetic blueprint.

NIH has made important progress in generating physical and genetic maps of the genome in the last year. These maps enable scientists to isolate and identify genes in order to study their function in health and disease. Scientists recently constructed physical maps for two human chromosomes: the human Y chromosome, found only in males; and the long arm of chromosome 21, which is associated with Down syndrome, and some types of Alzheimer's disease. An intense effort has been launched to study chromosome 17, which has particular importance in breast cancer and other hormonally mediated tumors. In all, about half of the markers needed to build a genetic map of the human genome have been identified.

Technologies developed within the *Human Genome Project* have already led to the discovery of many disease genes, including those for inherited forms of colon cancer and amyotrophic lateral sclerosis (Lou Gehrig's disease) and for fragile X syndrome, the most common genetic cause of mental retardation. This knowledge can aid scientists in developing molecular interventions that prevent or reduce the adverse effects of genetically related disease.



COMPUTERIZED VIEW OF LASER-EXCITED DNA BANDS ON AN AUTOMATED GENE SEQUENCER. THE SAMPLE IS FROM A PORTION OF THE CHROMSOME THAT CONTAINS THE HUNTINGTON'S DISEASE GENE.

The information generated by the *Human Genome Project* is expected to become the sourcebook for biomedical science in the 21st century. It will expedite progress in a variety of fields, including developmental biology and neurobiology. The analysis and interpretation of the wealth of data collected during this international effort will occupy scientists for many years to come. Yet the enormous potential of this project will be realized only if it is pursued in tandem with research focused on applying genetic information to prevent and treat disease.

The rapid evolution of genetics research makes it crucial for NIH to place greater emphasis on human molecular genetics in its intramural program. In order to create an intellectual and technological focus for fundamental genetics research at NIH, an intramural laboratory of human molecular genetics is being established, with a focus on disease genes, improved diagnostics, and gene therapy. This laboratory will enable the intramural NIH research community to participate in the *Human Genome Project*, making the technologies and knowledge it produces immediately accessible to intramural and extramural investigators. The successful completion of the *Human Genome Project* will be instrumental in guiding NIH in its efforts to understand and treat many of the more than 5,000 genetic diseases that afflict humankind, and other diseases and disorders in which genetic predisposition plays an important role.

Understanding the Molecular Basis of Disease

The explosion of knowledge about the regulation of normal and aberrant cell processes could lead to improved methods for intervening in a wide variety of diseases. Research on the molecular basis of disease will, in turn, identify potential targets for therapy. A related area of rapid progress is the molecular biology of the cell cycle. As the chemical processes controlling the growth of cells are elucidated, the results will be directly applicable to a wide variety of health problems.

Research on hormone and growth factor receptors, ion channels, transporters, and similar biological molecules affects virtually every institute and program involved in the biomedical sciences. The accessibility of these cell surface molecules — and the availability of new technologies that allow researchers to identify them rapidly and produce the agents that interact with them in amounts adequate for further studies — make these molecular entities attractive therapeutic targets.

Advances in molecular biology, protein chemistry, and structural biology are increasing our understanding of critical cellular factors implicated in human disease. The molecular basis of a disease state provides a foundation for developing specific therapies for effective treatment. Promising new approaches include the development of drugs designed to act upon specific cellular targets and the development of molecular and biochemical interventions for both prevention and therapy.

Human Gene Therapy

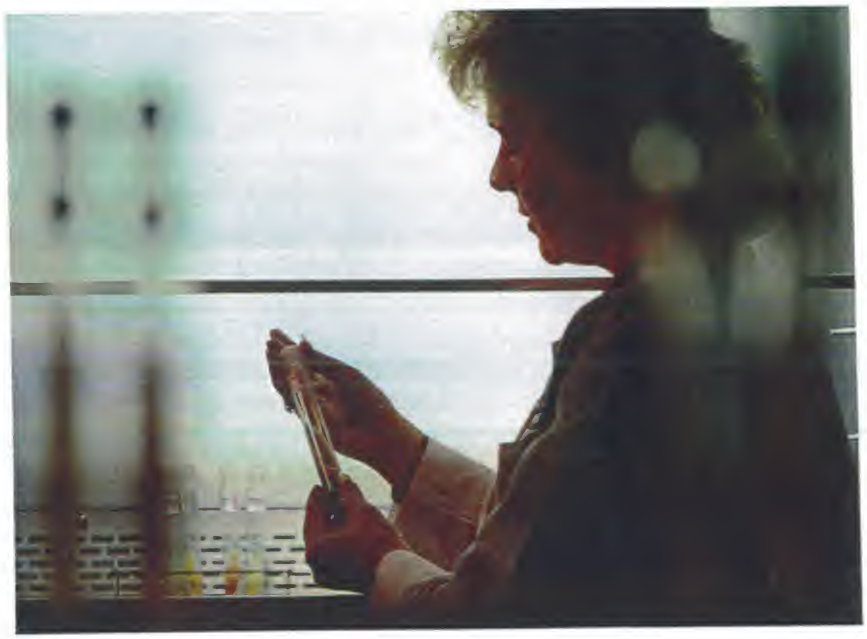
Gene therapy represents a revolutionary technological breakthrough in molecular medicine. It will ultimately give scientists the ability to manipulate the structure and function of genes, thereby offering tremendous potential to prevent, treat, and cure a broad range of diseases. Gene therapy encompasses several approaches, such as introducing specific genes, replacing defective genes, regulating gene expression, and developing molecular targets for disease therapy in living organisms and humans.

Sickle cell anemia, cystic fibrosis, neurofibromatosis, Huntington's disease, and Tay-Sachs disease are among some 5,000 genetic disorders caused by a single defective gene. Collectively, these genetic diseases have an enormous impact on society. For example, 3 percent of all infants in the United States have a genetic disease. These diseases account for 10 percent of all pediatric hospital admissions and 8.5 percent of all childhood deaths.

NIH has made dramatic progress in gene therapy research aimed at understanding and treating devastating inherited diseases. In 1990, NIH investigators performed the first clinical trial of gene therapy on a four-year-old girl who, like the "boy in the bubble," was prone to infections because of a mutation in the gene that encodes the enzyme adenosine deaminase. After treatment the child's health continues to improve, and she is now able to attend school for the first time.

Cancer, heart disease, chronic pulmonary diseases, mental illnesses, stroke, and substance abuse are among the many diseases that result from a combination of factors that includes our genetic makeup as well as environmental influences. Sadly, they account for the majority of deaths in this country and exact an enormous social and economic cost.

Human gene therapy promises new approaches to treat and cure many of these acquired or multifactor diseases. For example, a major new area of NIH-supported gene therapy research involves inserting altered genes into human tumor cells to enhance their tumor-killing capacity. In patients with advanced melanoma, results from preliminary clinical trials indicated a significant reduction in cancerous tumors after patients were injected with cells containing the gene for tumor necrosis factor. Preclinical and clinical trials involving gene therapy that are now underway at NIH are expected to serve as models for future clinical trials of engineered vaccines for breast, colon, ovarian, and renal cancers. Scientists are also developing techniques to implant genetically altered cells into the nervous system.



Isolating genes through recombinant DNA techniques.

Through greater understanding of the molecular mechanisms of normal cell growth and differentiation, and how cell processes are disrupted, scientists can design drugs specifically targeted to correct the abnormal metabolic and cellular processes associated with a particular disease. Promising approaches include the production and use of small synthetic molecular inhibitors such as peptide analogs and monoclonal antibodies, primarily in the treatment of cancer and neurological disease.

While clinical applications of gene therapy are underway, much remains to be learned to optimize our capacity to manipulate and control gene expression. NIH is committed to investing in basic molecular research that will advance gene therapy and the development of molecular therapies that target a specific disease.

Major Goals: Molecular Medicine

- *Complete the mapping and DNA sequencing goals of the* Human Genome Project.
- *Characterize the genetic components of complex diseases, including those linked to flaws in one or more genes, and apply this knowledge to develop new clinical therapies, including gene therapies.*
- *Identify molecular targets for new drug interventions in therapies for such diverse diseases as cancer, infections, and autoimmune disorders.*
- *Establish an intramural component to the National Center for Human Genome Research (NCHGR), which will develop a strong fundamental research program in gene discovery and gene therapy.*
- *Elevate NCHGR to the National Institute of Genomics and Medical Genetics.*
- *Facilitate research collaboration between basic and clinical science (at NIH and universities) and applied biotechnology (especially in the private sector) to advance rapid, large-scale production of new therapeutic agents.*
- *Identify interindividual variation in response to drugs and other chemicals for the purposes of identifying individual risk and developing tailored strategies.*

Biotechnology and Bioengineering

THE TREMENDOUS GROWTH AND SUCCESS OF THE U.S. BIOTECHNOLOGY INDUSTRY IS THE DIRECT RESULT OF A 45-YEAR INVESTMENT BY THE FEDERAL GOVERNMENT IN BIOMEDICAL RESEARCH, LARGELY SUPPORTED BY THE NATIONAL INSTITUTES OF HEALTH.

The products and technologies developed through this industry are significant, yet they pale in comparison to the discoveries we can expect in the future.

This decade will see unprecedented applications of biotechnology to agriculture and aquaculture, the environment, improved energy sources, and the development of drugs and technologies capable of improving human health. The impact of biotechnology on the Nation's economy will be enormous. In the next decade, for example, revenues from biotechnology products are expected to increase tenfold, skyrocketing to $50 billion by the turn of the century.

The talents, facilities, and resources of NIH are critical to the Nation's biotechnology industry. NIH has identified four initiatives as priorities because of their intrinsic importance to our mission. These initiatives have an added value in that they also hold particular promise for commercialization. These include:

- *Biological Response Modifiers and Monoclonal Antibodies*
- *Cellular and Tissue Engineering*
- *Transgenic and Other Animal Models*
- *Bioengineering*

Biological Response Modifiers and Monoclonal Antibodies

A number of biologically active natural proteins produced by recombinant technology and genetically altered proteins are already in use or in clinical trials or approved for treatment. Biological response modifiers (BRMs) are one example. By stimulating the production of healthy cells, BRMs have proven effective in the treatment of cancer and autoimmune, cardiovascular, and infectious diseases. BRMs have also been instrumental in prolonging patient survival from bone marrow and organ transplants. Research into these and other yet-to-be-discovered agents is of critical importance, given their potential contributions to the well-being of patients.

Cellular and Tissue Engineering

Cellular engineering can improve the function of living cells by manipulating enzyme, transport, and regulatory processes. This capability can have measurable results in disease treatment and intervention. To treat insulin-dependent diabetes, for example, scientists have moved closer to developing a genetically engineered pancreatic beta cell. These cells, created by splicing DNA into cells taken from the pituitary gland, produce insulin. Once scientists develop successful methods to regulate and transplant these engineered cells in patients, they may prove to be the most effective medical treatment to control insulin-dependent diabetes mellitus, dramatically improving the health and quality of life of diabetic patients.

Tissue engineering enables scientists to grow tissues and organs that serve as model systems in basic and applied research, and as grafts to replace diseased or damaged parts of the human body. For example, scientists have actually been able to grow skin cells and apply them as skin grafts that are particularly beneficial to burn victims.

In these areas, NIH has a strategic commitment to:

- Focus research on discovering ways to improve cell activity by manipulating the enzyme, transport, and regulatory processes of the cell.

- Develop "living tissue" equivalents such as an artificial liver, pancreas, and other artificial organs.

Transgenic and Other Animal Models

Many diseases and environmental toxins have effects on animals that are remarkably similar to their effects on humans. As a result, these "animal models" provide reliable systems for studying disease processes and environmental toxins and for developing new therapies. They can also become "bioreactors," producing medically important proteins and can facilitate studies on cardiovascular control mechanisms, neonatal hepatitis, mental illness, and drug addiction.

Transgenic animal models are produced by recombinant DNA techniques that eliminate, replace, or modify specific genes, as well as transfer genes into the genome of a host. These animals help researchers better understand the molecular abnormalities of acquired and inherited diseases that are caused by defects in single genes. With environmental and occupational exposures leading to increased incidence of genetic damage, transgenic animal models can provide insight into the nature of genetic damage as well as infectious diseases. For example, human immunodeficiency virus (HIV) infection with modified gene constructs can be examined in transgenic animals to study the pathophysiology of HIV-associated neuropathy, nephropathy, and the cachexia syndrome.

Bioengineering

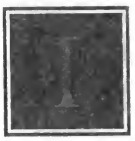
Advances in bioengineering are leading to the development of biomaterials, biosensors, biomechanical devices and instrumentation, and bioprostheses. For example, research is underway to develop a bedside sensor system for monitoring blood and urine chemistry. Investigation in the area of biomechanics has produced greater understanding of the nature of blood flow, joint movements, and locomotion, while providing the tools to design and manufacture such prostheses as artificial hips, kneecaps, and dental implants. In the field of neural prostheses, research has resulted in the development of a cochlear implant that provides some deaf individuals with the perception of sound.

Sophisticated instrumentation has enabled scientists to identify and characterize human tissue and to restore sensation and movement to a degree not thought possible a decade ago. One new system allows quadriplegics to grasp objects without assistance, and progress has been made on a prosthesis that may restore limited eyesight to the blind.

Major Goals: Biotechnology and Bioengineering

- *Elevate the priority of research on devices, biomaterials, diagnostic tools and prostheses.*
- *Develop improved biomaterials for orthopedic and dental use, replacement organs, and for nervous system injury.*
- *Accelerate the clinical applications of biological response modifiers and monoconal antibodies.*
- *Foster collaborations with the private sector and other government agencies with common interest in biotechnology.*
- *Establish cross-disciplinary research training programs in bioengineering.*
- *Develop a strong, effective infrastructure for the production, maintenance, and supply of genetically altered animals and other* in vitro *systems useful as models for disease and development.*
- *Evaluate the feasibility of an Interinstitute Center for Medical and Biological Engineeering.*

Immunology and Vaccines



Immune mechanisms, which enable the body to defend itself against viruses, bacteria, and other foreign organisms, are among our body's most remarkable biological strengths. The importance of the immune system in health and disease is increasingly understood by a public that has witnessed the devastating consequences of AIDS during the last decade.

The immunological tools of today — vaccines, monoclonal antibodies, and cytokines — are employed across every field of biomedical science and throughout medical practice. Research in the area of immunology and vaccines has led to numerous clinical applications.

Investment in immunology and vaccine research is the most cost-effective approach for preventing disease. In 1992 alone, more than 80 percent of the world's children were vaccinated against one or more common childhood illnesses, saving an estimated 3 million lives. Now the challenge is even greater: to develop a vaccine for AIDS and other complex diseases of the immune system — rheumatoid arthritis, myasthenia gravis, multiple sclerosis, and psoriasis — which mount an attack against the body's own cells.

The development of effective vaccines and interventions for these immune diseases will require greater understanding of how the immune system works, the pathogenesis of infectious organisms, and how the immune system can be manipulated to protect the body from disease. Vaccines against infectious diseases that predispose individuals to certain cancers are now within reach. Also at hand are vaccines that offer novel approaches to birth control and allergies.

Current concerns about liability have delayed the development of several promising AIDS vaccines. Manufacturers and researchers are finding it difficult or impossible to obtain insurance against AIDS vaccine-related injuries. Although NIH does not typically become involved in the later stages of drug development, these concerns require that NIH take a leadership role in supporting and advancing vaccine research. Initiatives to support this priority include:

- *Vaccine Project Against Human Disease*
- *Understanding Host-Pathogen Interactions*

Vaccine Project Against Human Disease

NIH recognizes the capacity of the biomedical research community to address urgent issues in vaccine development. To accelerate the creation of new vaccines and expand the science on which they depend, NIH proposes to establish a collaborative *Vaccine Project Against Human Disease*. Capitalizing on an existing network of talented, dedicated investigators involved in vaccine and immunologic research, this initiative seeks to identify institutions with expertise and interest in human vaccine development. These scientists will form a consortium devoted to developing safe, effective vaccines for the following diseases:

EXAMINING PETRI DISHES CONTAINING BACTERIA INFECTED WITH A VIRUS ENGINEERED BY RECOMBINANT-DNA TECHNOLOGY.

■ *New and Emerging Infectious Diseases* — These diseases include HIV infection, which currently affects an estimated one to two million people in the United States; tuberculosis, with a rising incidence in the United States; and sexually transmitted diseases.

■ *Cancer* — Recent developments in cellular immunology and biotechnology have led to the development of immunization approaches for the treatment and prevention of cancer. Preclinical studies have demonstrated the effectiveness of recombinant vaccines for gastrointestinal cancers and melanoma. Research is also underway to develop a human papilloma virus vaccine to prevent cervical cancer.

■ *Immunologic and Allergic Diseases* — The development of immunoprevention therapies will benefit individuals with allergies, asthma, and autoimmune diseases such as diabetes mellitus, multiple sclerosis, and lupus.

An investment in immunology and vaccine research will translate into millions of lives saved — and millions of dollars saved — in health care and medical costs associated with these life-threatening diseases.

UNDERSTANDING HOST-PATHOGEN INTERACTIONS

The human body cannot survive without the immune system, a complex, finely tuned network of molecular defenses such as lymphocytes and antibodies, which protect the body against foreign organisms, including viruses and bacteria. The immune system also plays an integral role in monitoring the emergence of aberrant cells that can produce the myriad cancers.

The immune system is intricately involved in many common and devastating diseases, including tooth decay, the common cold, tuberculosis, pneumonia, AIDS, rheumatoid arthritis, and lupus. Only through fundamental understanding of the immune system's function and the mechanisms by which foreign organisms attack and invade host cells, survive resistance, grow, spread, and move into new hosts, can scientists develop drugs and vaccines capable of selectively blocking infection or disease. In turn, these medical breakthroughs promise to save the lives of millions of people in the United States and worldwide.

Greater understanding of the mechanisms responsible for discrimination between self and foreign antigens, and how cells respond to different antigens, is critical if scientists are to continue expanding our understanding and treatment of autoimmune diseases and cancer. Scientists must also learn more about the protective mechanisms of the immune system. With such advances, it will be possible to safely manipulate the immune system to prevent and treat disease.

In this area, NIH supports basic research to further understand the pathogenesis of disease and the interactions between the host cell and the pathogen — the foreign organism — that lead to health or disease. Among its research priorities are the following: enhancing understanding of the molecular basis of antigen recognition, function, and regulation; examining age-related changes in immune cell function and regulation of the immune response; studying gene regulation in immune cells; and developing vaccines against specific diseases and conditions, including the use of vaccines in fertility regulation.

Historically, vaccine development has relied on the identification of an antigen, usually a protein or carbohydrate capable of stimulating an immune response, that could be used to prepare a vaccine. The biotechnology revolution has given new life to vaccine development, opening the door to an array of new "engineered" vaccines that are safe and effective, such as those envisioned by the Children's Vaccine Initiative. The number of infections and other diseases affecting both children and adults that can now be prevented or treated using vaccines is large and continues to grow. Nonetheless, basic research into the process by which antigens prevent or treat disease must be strengthened.

Major Goals: Immunology and Vaccines

- *Expand fundamental understanding of the immune system and its complex role in health and disease.*
- *Develop more effective therapeutic approaches against infectious and autoimmune diseases such as AIDS, multiple sclerosis, and lupus.*
- *Work with policy makers in government and industry to resolve HIV and other vaccine liability issues.*
- *Launch the* Vaccine Project Against Human Disease *consortium.*

Shape. Form. Structure. These concepts are now more vital than ever in biomedical research and the effort to treat and prevent human diseases. A new hybrid of scientific endeavor — "structural biology" — blends physical and biological research in remarkable and beneficial ways. We now have the ability to visualize in precise detail the three-dimensional molecular architecture of proteins and other biologically important molecules, providing critical insights into their function. Such insights can speed the development of vaccines to prevent devastating viral infections such as AIDS and drugs to arrest cancer and other killer diseases. Structural biology, which underpins all areas of NIH-supported biomedical research, is a linchpin in U.S. biotechnology research efforts.

NIH is undertaking a *Human Cell Initiative* to describe, in complete detail, the macromolecular and supramolecular structure of the human cell. This complements the interinstitute collaborations in cell biology (see page 30). An understanding of cell structure is a critical step in defining the parameters that regulate cell function and how defects in the macromolecular assembly lead to disease. Ultimately this knowledge will be translated into new therapeutic approaches.

Through the proposed *Human Cell Initiative*, NIH will make a strategic commitment to advance understanding of the function of proteins and other molecules, develop instruments and technologies in the field accessible to scientists, and enhance computer-based technologies to facilitate research in this area. In effect, the *Human Cell Initiative* builds upon the *Human Genome Project* by exploring, from a broader perspective, how cells function. There are three components to the *Human Cell Initiative*:

- Macromolecular Assembly Systems
- Structure-Based Drug Design
- Technology and Instrumentation

Macromolecular Assembly Systems

For life to exist, its building blocks—including proteins and nucleic acids—must combine into more complex structures. Understanding the structure and function of such "macromolecular assembly systems" will assist in understanding cellular processes, paving the way for new clinical therapies for a spectrum of diseases. This initiative exploits the current revolutions in molecular biology and genetic engineering. Technologies that can produce large amounts of proteins for examination by X-ray crystallography, together with the increasing power of the techniques of structural biology, will further our understanding of the molecular interactions involved in the binding of proteins with other biopolymers. Determination of the structure of macromolecular assemblies will require adapting existing technologies and developing new ones.

Structure-Based Drug Design

Knowledge of the three-dimensional structure of a pharmacologically significant enzyme or receptor site can accelerate the discovery and enhancement of therapeutic drugs. An effective treatment for disease may result from combining this knowledge with computer modeling programs to produce chemical structures that inhibit molecular dysfunction with enhanced specificity.

Technological advances in X-ray crystallography and nuclear magnetic resonance spectroscopy have far-reaching implications for the design of structure-based drugs. For example, X-ray crystallography enabled scientists to determine the complete, three-dimensional architecture of the virus that causes the common cold (rhinovirus). This finding raises the possibility of synthesizing a molecule that would block the rhinovirus by binding to its receptor site, thereby preventing it from attaching to its target cell. This could lead to an effective therapy for the common cold.

NIH recognizes that further advances in structure-based drug design will require, among other critical resources, improved methods of recombinant DNA technology for cloning and producing large quantities of target proteins; advanced separation and synthesis capabilities to purify these proteins; greater availability and access to sophisticated research technology in individual laboratories; and national or regional facilities that allow scientists to view and study the three-dimensional structure of biologically important molecules.

Computer-generated 3-D image of protein molecule.

Technology and Instrumentation

A series of new technologies and highly sensitive instruments have advanced our understanding of the molecular basis of cellular function and breakdown. X-ray diffraction analysis, synchrotron radiation and x-ray crystallography, nuclear magnetic resonance, mass spectrometry, and electron microscopy have revealed the structures of proteins, nucleic acids, and macromolecular assemblies. Other new approaches have now breached the limits of classical diffraction optics.

Structural biology remains firmly based on research in individual laboratories, but it is becoming increasingly clear that advances depend on expensive technologies and, thus, collaboration among research groups. Some capabilities can be provided only through national or regional facilities because of cost or complexity. Many other essential technologies are initially developed at major centers and later become accessible to individual laboratories. Nevertheless, new instruments and technologies must be available, if only on a centralized basis, for the recent achievements in structural biology are to continue. Accordingly, we must develop the means to create and extend these techniques of structural biology.

Major Goals: Structural Biology

- *Design and establish the* Human Cell Initiative
- *Enhance availability of research technology, both in individual laboratories and through national or regional facilities, and access to high-performance computing and communication.*
- *Develop methods for obtaining suitable crystals of target proteins, particularly those that are associated with the cell membrane.*
- *Intensify research in the application of novel instrumentation and computational techniques to structure-based design of new drugs.*
- *Enhance training of investigators capable of bridging the multidisciplinary approaches of structural biology — applied physics, chemistry, electrical engineering, computer science, biochemistry, and biology.*
- *Establish and expand databases of solved protein structures, readily accessible to investigators.*

Cellular and Integrative Biology

The cell is a fundamental unit of living matter. Alone and in concert with other cells, it performs all the fundamental processes that make human life possible. An explosion in our understanding of the biology of the cell has laid the groundwork for novel, effective interventions to prevent and treat disease.

Our capacity to use and manipulate cells in the treatment of disease requires greater understanding of how cells grow and proliferate, how they differ from one another, how they interact with one another to form tissue and organs, and how they respond to the environment and other outside influences. Two areas of primary importance are cell biology and the neurosciences.

A complex problem for scientists, only now beginning to yield new research approaches, is to understand how a single, undifferentiated cell miraculously develops into a complex human being. NIH believes research in these areas will lead to new therapies for disease — some predicted, some hoped for, some presently unimagined.

Equally complex is understanding the basis for acquiring, processing, storing, and retrieving information by the central nervous system. This information will profoundly affect our ability to understand the fundamental processes of sensory perception, learning, cognition, behavior, and memory. It also will serve as the basis for new approaches to sensory deficits, learning disabilities, memory disorders, coordination and movement disorders, and behavioral and psychiatric problems.

Research initiatives of strategic importance to NIH include:

- *Interinstitute Collaborations in Cell Biology*
- *Human Brain Initiative*

Interinstitute Collaborations in Cell Biology

As the structural unit of biology, the cell is central to the study of the physiology and pathology of the human body. The field of cell biology seeks to describe biological processes within the context of intracellular structures and interactions. Cell biology explains the functions of gene products; illuminates the processes that determine the growth, differentiation, and aging of cells and organisms; and enables us to understand and manipulate the interactions of an organism with its environment. Cell biology is, in fact, fundamental to the research conducted and supported by all of the institutes of the NIH.

The NIH intramural program, with its unique capacity to draw on the knowledge and talents of a diverse group of scientists interacting with one another in a single location, intends to be a major center for the study of the cell. As part of the *Human Cell Initiative* Interinstitute Collaborations in cell biology will be established that will serve as a focal point for discovery, training, collaboration, and resource sharing by intramural scientists, eventually from all of the institutes. This trans-NIH initiative will embrace the research activities of several institutes and will allow investigators to translate their discoveries in cell biology into new therapies and prevention strategies.

The *Human Cell Initiative* also encompasses developmental biology. A better understanding of embryogenesis — cell development and specialization — will bring scientists closer to creating effective therapies for a wide range of human disorders. Insofar as this research expands our fundamental understanding of multi-cellular

communication and how cells interact to form tissues and organs, it may lead to new strategies for repairing or replacing tissues and organs. For example, cell and tissue transplantation may help patients recover from injuries to the central nervous system, spinal cord, muscles, ligaments, skeleton, and other organ systems. In addition, cell transplantation may also prove efficacious in treating neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, as well as mental illnesses, such as schizophrenia.

Human Brain Initiative

The 1990s have been proclaimed the "Decade of the Brain," a time when scientists stand to make dramatic progress in understanding the complexities of the brain and the nature of brain disorders that afflict millions of Americans. In this decade and into the next century, scientists are poised to increase understanding of the brain's complex anatomy, chemistry, and function, and to develop new therapies aimed at preventing and treating brain disorders.

The *Human Brain Initiative* is designed to increase our understanding of the development of the brain and behavior across the life span. It is likely to yield new ways to help children overcome physical, emotional, and learning disabilities; free young adults from the ravages of mental, addictive, traumatic, neuromuscular, and sensory disorders; and allow the elderly to enjoy a fuller measure of health and independence.

Because of the wide range of conditions that can be traced to processes in the central and peripheral nervous systems, basic research in the neurosciences will be a central focus of this initiative. Opportunities include the function, organization, and interaction of brain neurons and the genetic and environmental determinants of brain development, plasticity, and function. Resources will also be needed for long-term primate studies of pathological and compensatory changes, and for advanced imaging and modeling techniques. Research will also focus on the neural basis for sensory processing, learning, and memory.

Major Goals: Cellular and Integrative Biology

- *Establish interinstitute collaborations in cell biology within the intramural research program of NIH, which will provide centralized resources for macromolecular sequencing and synthesis.*
- *Establish the* Human Brain Initiative, *which will include developing computerized models to elucidate the organization and complex activity of the billions of brain neurons. It will also facilitate the integration of such fields as synthetic chemistry, cell biology, physiology, the neurosciences, imaging biophysics, and computation with molecular genetics to accelerate basic research findings and clinical therapies.*
- *Expand fundamental understanding of the architecture of cells and tissues, the biochemical basis for cell growth, and the genetic basis for cell development and differentiation.*
- *Apply new scientific insights in embryogenesis, development, and cell specialization to clinical treatment of spinal cord injuries, diabetes, and Alzheimer's and Parkinson's disease.*
- *Explore the feasibility of establishing extramural Interinstitute Specialized Centers of Research for Cell Biology.*

Critical Health Needs

The health of nations is more important than the wealth of nations.

— Will Durant, American historian

The Nation's research enterprise must strengthen its ability to address current and emerging public health needs. NIH responds to these needs in two ways. Our traditional approach uses NIH's individual institutes to address specific diseases and disorders, such as cancer, heart disease, and mental illness. Two new initiatives use this same disease-specific approach to address the emerging threats of AIDS and drug-resistant tuberculosis. A companion approach cuts across the institutes and centers to promote general health and disease prevention.

Part I:
NIH Initiatives to Combat Disease through Its Component Institutes

The institute structure is the primary means by which NIH responds to the critical public health needs that involve specific diseases and disorders. The following are the strategic components of NIH: (date indicates year institute was established)

National Cancer Institute (NCI) (1937)

NCI leads a national endeavor to prevent and cure cancer. Newly discovered strategies include insertion of genetic material into target cells to correct inherited genetic errors or acquired mutations that have caused cancer or to confer new functions to cells for use in fighting disease. Promising new anticancer drugs such as taxol, an agent active against ovarian, breast, and lung cancer, are being tested, often in collaboration with industry. Research is directed at learning to manipulate cancer genes, suppressor genes, cell cycle regulators and growth factors; developing anticancer vaccines; increasing understanding of environmental causes of cancer, including lifestyle and other factors; and implementing new approaches to prevent cancer through chemopreventive agents, behavioral interventions, and other means.

National Institute of Mental Health (NIMH) (1946)

NIMH exerts leadership on behalf of all mentally ill citizens by creating a scientific foundation for the clinical care of mental disorders; by developing innovative approaches to diagnosis, treatment, and prevention of mental illnesses; and, by translating that knowledge into practice. NIMH supports basic brain research and clinical and services research into the biological, psychological, behavioral, and epidemiological aspects of mental illnesses, disorders that affect one out of every four Americans. Past research has led to improved brain imaging technologies, new drug therapies based on brain neurotransmitter and receptor systems, better psychosocial treatments, and improved understanding of mental health services. Future research will target the genetic, molecular, behavioral, and environmental factors important in the development of mental illnesses and their treatments.

National Heart, Lung, and Blood Institute (NHLBI)(1948)

NHLBI provides leadership for a national research program in diseases of the heart, blood vessels, lungs, and blood and in transfusion medicine through support of innovative basic, clinical and population-based, and education research. Remarkable advances have enhanced our understanding of heart attack and improved its treatment; led to the development of safe, effective therapy for respiratory disorders such as respiratory distress syndrome in infants; and improved our knowledge of hemoglobin, leading to better health for patients with sickle cell disease and Cooley's anemia. Future research will focus on the genetic basis and gene therapies for a number of serious hereditary diseases, as well as factors that predispose individuals to develop cardiovascular, pulmonary, and blood diseases across the life span.

National Institute of Dental Research (NIDR) (1948)

NIDR investigators study disease and disorders of the teeth, mouth, jaws, and face; the normal process of oral and facial development; and how oral health is related to general health. Prevention is the Institute's highest priority. For example, the use of flourides has vastly improved the dental health of Americans. Recent research has identified the genes responsible for some forms of cleft palate and other birth defects, as well as a factor involved in new bone growth. Goals for the future include the further reduction of dental and oral diseases through the application of cell and molecular biology technology to diagnosis, treatment, and prevention.

National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (1948)

NIDDK conducts and supports research on many chronic and serious diseases that affect public health. Research areas recently emphasized by the Institute include the molecular biology of diabetes and cystic fibrosis; digestive diseases and nutrition; obesity and its relation to other chronic diseases; fundamental and clinical research on osteoporosis; kidney diseases generally, and kidney disease and hypertension in African Americans in particular; and urologic diseases such as benign prostate disease and interstitial cystitis. Successes in these areas position the Institute for future research that includes the genetics of diabetes, gene therapy for cystic fibrosis, mechanisms and treatment of obesity, and basic and clinical studies of urological disorders.

National Institute of Allergy and Infectious Diseases (NIAID)(1948)

Researchers at NIAID strive to understand, treat, and ultimately prevent the myriad infectious, immunologic, and allergic diseases that threaten millions of human lives. Among their recent successes are development of an improved vaccine against whooping cough, methods to lower rejection rates for transplanted organs, and development of treatments providing longer, better lives for people infected with HIV. Future goals include the development of vaccines against a number of infectious diseases, particularly childhood diseases, sexually transmitted diseases, and AIDS, as well as improved therapies for asthma and autoimmune disorders.

National Institute of Neurological Disorders and Stroke (NINDS) (1950)

NINDS seeks to understand the brain and the neurological foundations of more than 600 disorders that strike 50 million Americans each year. Stroke, for example, is the third leading cause of death in the United States. In the past, NINDS has developed treatments for preventing stroke in patients with cardiovascular disease, controlling the early stages of Parkinson's disease, and improving recovery after spinal cord injury. Targets for future research include the causes, prevention, and therapies for conditions such as Alzheimer's disease, epilepsy, head injury, and cognitive disorders.

National Institute of General Medical Sciences (NIGMS)(1958)

NIGMS supports basic biomedical research that is not targeted to specific diseases or disorders. Among the most significant results of this research has been the development of recombinant DNA technology, which forms the basis for the biotechnology industry. Other advances include improved understanding of the relationship between protein structure and function, greater knowledge about the cell, and increased understanding of synthetic chemistry. Research training is central to the institute's mission: NIGMS supports multidisciplinary training programs, as well as programs to train physician-scientists and programs to increase the number of minority biomedical scientists.

Fogarty International Center for Advanced Study in the Health Sciences (FIC)(1960)

Widespread transmission of infectious diseases, the emergence of new and more virulent diseases, skyrocketing costs, and increasing demands for human resources have made international cooperation in biomedical research imperative. As the organizational focus for NIH's international activities, FIC promotes collaborative research on the causes and prevention of diseases of global impact, such as AIDS and other emerging diseases; supports broader access to new information and techniques, such as molecular approaches to drugs and diagnostics; and takes advantage of the opportunities presented by geopolitical change, including regional initiatives in Eastern Europe, the former Soviet Union, and the developing world.

National Institute of Child Health and Human Development (NICHD)(1963)

NICHD research on fertility, pregnancy, growth, development, and medical rehabilitation strives to ensure that every child is born healthy and wanted, and grows up free from disease and disability. Among NICHD discoveries are a genetic mutation that causes infertility and a vaccine that may eliminate a major cause of mental retardation and deafness in children. Future NICHD goals include further reductions in infant morbidity and mortality, improved ability to regulate fertility, and new rehabilitation techniques to compensate for physical and mental disabilities.

National Institute of Environmental Health Sciences (NIEHS)(1966)

Human health and human disease result from three interactive elements: individual genetic susceptibility; environmental factors; and time. The NIEHS mission is to enhance the understanding of each of these elements and how they interrelate, thus leading to a reduction in the burden of human illness and dysfunction from environmental causes. Examples of diseases that have an environmental component in their etiology include cancer, neurological deficits, respiratory disorders, and birth defects. NIEHS achieves its mission through a multidisciplinary biomedical research program, prevention and intervention efforts, and a communication strategy that encompasses training, education, technology transfer, and community outreach.

National Eye Institute (NEI)(1968)

Diseases of the eye and visual system debilitate millions of Americans. NEI-supported basic and clinical research has resulted in significant advances in the diagnosis, treatment, and understanding of eye diseases and vision disorders such as diabetic retinopathy, glaucoma, cytomegalovirus retinitis, ocular herpes, and retinitis pigmentosa. Future research into basic disease mechanisms may lead to the means of preventing or delaying sight-threatening diseases of aging, such as age-related macular degeneration and cataract, or to more effective treatments of disorders of the central visual pathways, such as optic and retrobulbar neuritis.

National Institute of Alcohol Abuse and Alcoholism (NIAAA)(1970)

NIAAA is conducting research focused on improving the treatment and prevention of alcoholism and alcohol-related problems to reduce the enormous health, social, and economic consequences of this disease. Its research program, encompassing a wide range of biomedical and behavioral disciplines, has led to a number of recent scientific accomplishments in the neurosciences, genetics, and molecular biology, and to identification of fetal alcohol syndrome. Future priorities include the expanded study of genetics to identify the gene or genes that influence susceptibility to alcohol, development and assessment of new medications to reduce craving and prevent relapse, and expanded prevention studies and clinical trials of combined psychosocial and pharmacological interventions to enhance treatment outcomes.

National Institute on Drug Abuse (NIDA)(1972)

NIDA provides national leadership for research on drug abuse and addiction. NIDA research focuses on the causes, consequences, prevention, and treatment of drug abuse and addiction, as well as its biological, social, behavioral, and neurological bases. Past research has identified the discovery of endogenous opioid peptides and receptors, which led to the development of several drugs that block the effects of opiates and thereby allow for rapid and effective medically assisted withdrawal. Research will continue to include both the biological and behavioral bases of drug abuse to facilitate the development of more effective approaches to prevention and treatment. Special emphasis will be given to halting the spread of HIV among drug abusing populations and providing effective treatment for pregnant addicts with minimal effects on the fetus.

National Institute on Aging (NIA)(1974)

NIA leads a national program of research on the biomedical, social, and behavioral aspects of the aging process; the prevention of age-related diseases and disabilities; and the promotion of a better quality of life for all older Americans. Major research advances have been made in specifying the molecular and genetic basis of Alzheimer's disease; identifying a therapy that significantly reduces the incidence of stroke and cardiovascular disease in older persons with isolated systolic hypertension; and discovering a method to increase the accuracy of early detection of prostate cancer. Future research will target the molecular genetic basis of longevity and aging, and basic and clinical studies of Alzheimer's disease, frailty, osteoporosis, cancer, cardiovascular disease, and other age-related diseases and disorders.

National Institute for Nursing Research (NINR)(1986)

Through NINR-sponsored research, nurse-scientists are discovering new ways to promote health, prevent disease, and minimize the effects of illness and disability. Research has led to new approaches to patient care that lessen the adverse effects of chemotherapy, enhance the treatment and evaluation of premature and low-birth-weight babies, and improve the quality of life of Alzheimer's patients. Future research will focus on health promotion for children and adolescents, clinical problems in women's health and long-term care, and prevention and treatment of symptoms (e.g., pain and fatigue) that impair quality of life for patients and informal caregivers.

National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS)(1986)

NIAMS supports basic and clinical research on the structure and function of joints, bones, muscles, and skin. Its research in rheumatology, bone diseases, orthopedics, dermatology, and sports medicine has led to breakthroughs in the diagnosis, treatment, and prevention of many of the most debilitating diseases, including osteoporosis, arthritis, and lupus. Future goals include identifying the genetic risk factors and molecular mechanisms associated with these disorders, and developing more effective prevention and treatment programs based on this fundamental knowledge.

National Institute on Deafness and Other Communications Disorders (NIDCD)(1988)

NIDCD conducts and supports biomedical and behavioral research and research training on normal mechanisms as well as diseases and disorders of hearing, balance, smell, taste, voice, speech, and language that affect 46 million Americans. NIDCD also supports efforts to create devices that substitute for lost and impaired sensory and communications functions and address the special problems of people with communications disorders. Considerable progress has been made on noise-induced hearing loss and viral infections of the inner ear, as well as sensory cell regeneration and acquisition of both signed and spoken language. Critical goals for future research include identifying the genes for hereditary hearing impairment, stuttering, and dyslexia; providing early detection of hearing loss in infants; making progress in the treatment of aphasia; and developing a vaccine for the prevention of middle ear infections.

National Center for Human Genome Research (NCHGR)(1990)

NCHGR is the NIH component of the Human Genome Project (HGP), a worldwide research effort designed to analyze the structure of human DNA and determine the location of the estimated 100,000 human genes. HGP has already isolated the genes for several hereditary diseases, and since virtually every component of NIH supports genetic research, the future fruits of this effort should be even more dramatic. Five-year goals include improved sequencing technology to reduce costs, maps of human chromosomes, computer databases to provide wider access to research information, and attention to the ethical, legal, and social implications of genome research. This Center is expected to evolve into the National Institute of Human Genetics.

To augment the institute efforts, NIH has also used other mechanisms to combat the disease-specific emerging health crises of AIDS and drug-resistant tuberculosis.

Office of AIDS Research

The NIH Office of AIDS Research (OAR) has been given broad new legislative authority to orchestrate a fully coordinated research assault on AIDS. Working closely with the institutes and outside experts, OAR will develop a strategic plan to guide NIH's HIV-related research efforts. That plan will address emerging scientific opportunities; reflect and respond to the changing demographics of the epidemic; integrate basic, clinical, and behavioral research; and further the principles contained in the NIH Strategic Plan. The OAR plan will be regularly updated and will form the framework for annual budget formulation.

The expanded authority is intended to improve NIH's response to scientific opportunities and gaps in knowledge. OAR will establish coordinating groups for each of the various research disciplines: etiology and pathogenesis; natural history and epidemiology; therapeutics; vaccines; and behavioral research to assure coordination of research across the institutes. These efforts will be tightly linked to a consolidated annual AIDS budget that will be transmitted directly to the President.

This congressional mandate also gives OAR authority to hire research personnel needed to conduct a wide range of AIDS-related research activities within the institutes. Moreover, a discretionary fund for AIDS research will provide OAR the capability to respond rapidly to emergencies and critical gaps in research.

With the new flexibility and added authority of OAR, NIH can design and implement complementary research initiatives that help the Nation and the world address this deadly public health crisis.

Drug-Resistant Tuberculosis

The NIH research enterprise needs budgetary flexibility to respond rapidly to emerging threats to public health. NIH's research strategy to combat the threat of drug-resistant tuberculosis (TB) marks the first use of NIH's emergency budget reallocation authority to respond to a health crisis.

After decades of decline, there has been a resurgence in the incidence of TB in the United States. Over 26,000 active cases were recorded in 1991, up 18 percent since 1985. As many as 15 million Americans have latent infections that could be reactivated, and because the TB bacillus is so easily transmitted through airborne droplets, everyone is potentially at risk to contract this disease. Especially troubling is the appearance of new strains of the disease that are resistant to drugs used in the past.

NIH has responded to this public health threat with a comprehensive research strategy:

Basic Biological Research — Targets include the mechanisms by which Mycobacterium tuberculosis causes disease, the factors involved in latency and reactivation, the mechanisms of drug resistance, and development of new diagnostic tools, new therapies, and drug-delivery systems.

Clinical Trials and Population-Based Studies — Additional clinical trials will be initiated to evaluate drugs and other interventions for classic TB and drug-resistant TB.

Vaccine Development — The current TB vaccine is unreliable, and it causes a false positive TB skin test. NIH will expand efforts to develop new TB vaccines.

Compliance Research – Behavioral methodologies must be developed to ensure that patients complete their treatment regimens and to prevent the emergence of further drug-resistant strains. Special measures may be needed for populations such as drug addicts, who have the highest incidence of HIV and the lowest level of compliance in the absence of intervention.

Training and Facilities — A new cadre of biomedical researchers must be directed toward this effort through retraining and career development. These investigators will need special laboratories designed to prevent release of airborne, infectious agents.

Educating Health Care Workers and the Public — The public education campaign must be aimed at the general public and vulnerable populations, including health workers.

Part II:
NIH Initiatives to Promote General Health and Disease Prevention

Many critical health needs are broader and more general than a single disease or disorder. The Strategic Plan identifies major cross-cutting areas of basic and clinical research that are crucial to NIH's mission of improving general health and preventing disease. The following areas of emphasis and initiatives, which demonstrate NIH's strong, unified approach at the trans-NIH level, will enhance our ability to address current and emerging threats to public health.

The environment, our genetic makeup, and time interact to determine our predisposition to good health or disease. Understanding how these factors converge and their consequences for human health is vital in reducing the risk and incidence of disease and in developing strategies for prevention and intervention.

Environmental factors include diet, natural chemicals, radiation, micro-organisms, stress — even the socioeconomic conditions in which people live. Understanding how these environmental elements influence health is enormously complicated by genetic factors. Our genes determine our susceptibility to various environmental agents and their ability to disrupt biological activity in the human body. These susceptibilities rise and fall at various times in the life cycle. For example, environmental agents that produce genetic disorders during fetal development are benign at other times of life.

The complex interaction between environmental and genetic factors makes it essential that NIH commit its resources to research that explores this interaction at its most fundamental level — genes and the proteins they encode. Specific research initiatives of high priority for NIH include:

- *Effects of Environmental Agents on Genes and Gene Products*
- *Environmental Effects on Cell Function, Communication, and Regulation*
- *Environmental Effects on Integrated Biological Systems*
- *Individual Susceptibility to Environmentally Caused Diseases and Dysfunctions*

Effects of Environmental Agents on Genes and Gene Products

Genes, the basic building blocks of cell function, direct all biological events from conception to death. When DNA is damaged, gene function may be impaired, and with it human health. Birth defects, cancer, neurological dysfunction, infertility, and immune dysfunction are among thousands of disorders and diseases associated with genetic flaws.

Scientists have identified numerous environmental agents, such as chemicals and radiation, that interact with and damage DNA. Yet linking these agents to specific diseases is complicated by the fact that considerable time can elapse between exposure and the actual appearance of disease. NIH supports research on a broad spectrum of diseases and disorders suspected of having a potential environmental component. Such efforts will not only identify harmful environmental agents, but also help to reduce or eliminate the risk of exposure.

Environmental Effects on Cell Function, Communication, and Regulation

The "genetic model" has proven valid for explaining the role of some environmental agents in diseases such as birth defects and cancer. However, many chemical teratogens and carcinogens interact, not with DNA, but at the next level of cellular organization — the protein encoded by an individual gene. Identifying the role of individual protein messengers and receptors in cellular functions may help us to explore the ability of environmental chemicals to interact with these critical proteins in a host of diseases and dysfunc-

A researcher examines amphibian eggs. These types of studies can be used to detect changes due to environmental agents.

tions, including infertility, birth defects, neurological disorders, immune dysfunctions, and chronic disease.

Environmental Effects on Integrated Biological Systems

Once we have improved our understanding of the basic building blocks of molecular and cellular systems and their interactions with environmental agents, we must integrate these single systems into multisystem studies. Understanding the interdependence among systems is particularly important in studying the environmental causes of disease. An environmental agent that adversely affects one organ system can secondarily affect other organ systems that communicate with it.

Individual Susceptibility to Environmentally Caused Diseases and Dysfunctions

Scientists have growing evidence that individuals react in widely different ways to environmental chemicals. Genetics, gender, age, underlying chronic diseases, and nutrition must be explored to determine their impact on enhancing environmental diseases or protecting an individual from the effects of environmental agents. Collaborative research, involving epidemiologists and molecular biologists, is needed to evaluate the factors responsible for individual variations. Such research promises to improve our ability to prevent health problems caused by exposure to environmental agents, as well as to identify those individuals who are at greatest risk.

Major Goals: Basic Biology Related to the Environment

- *Attract more extramural investigators into the field of environmental health sciences by tripling the portfolio of individual investigator grants within three years.*
- *Establish a Mouse Genome Project, DNA Bank, and Disease Registry that will collect and collate information generated by research on the effects of environmental toxins on DNA.*
- *Identify the critical genes and gene products, cellular receptors and pathways, multisystem perturbations, and individual factors that are involved in the environmental contribution to dysfunction leading to human disease and disability.*
- *Establish an emergency response mechanism to address newly identified environmental threats. This would include mobilizing resources within and outside NIH in a coordinated fashion.*

EHAVIOR AND LIFESTYLE FACTORS, FROM DIET AND SMOKING TO SEXUAL PRACTICES AND ALCOHOL ABUSE, CONTRIBUTE TO MAJOR PUBLIC HEALTH PROBLEMS IN OUR SOCIETY. IN FACT, LIFESTYLE FACTORS UNDERLIE THE 10 LEADING CAUSES OF DISEASE AND DEATH IN THE UNITED States, including heart disorders, cancer, diabetes, and sexually transmitted diseases including AIDS. Behavior is linked to disease in several ways: as its cause or as a risk factor (e.g., alcohol, drugs, smoking); as a co-factor in its progression; as a consequence of illness when depression, anxiety, or substance abuse may also occur; and as a method of treatment and prevention.

Mental and addictive disorders, neurological diseases, sensory and communication deficits, and developmental and aging problems underscore the influence of the brain on behavior and health. These complex public health problems point to the need for multidisciplinary approaches that combine the knowledge and techniques of molecular biology, structural biology, the neurosciences, and the behavioral sciences to increase our understanding of human behavior and how it affects health and disease in the United States.

Initiatives in the area of behavior and health include:

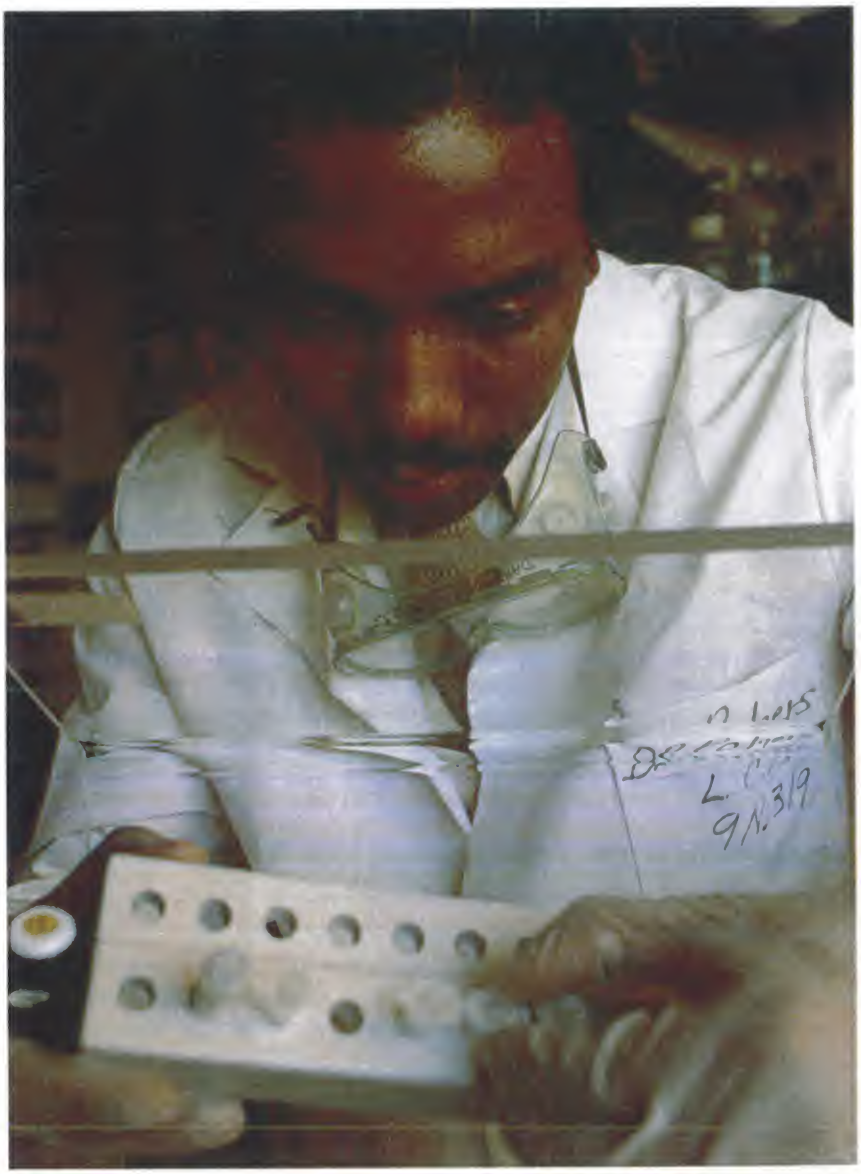
- *Neuroscience and Behavior*
- *Behavior and Health Across the Life Span: Biobehavioral Medicine*

NEUROSCIENCE AND BEHAVIOR

An estimated 75 million people are affected each year by disabilities and disorders that involve the nervous system. The people who have these disorders, and those who care for them, carry a great emotional and economic burden. Our goal is to develop better ways to diagnose, prevent, and treat the broad spectrum of diseases that compromise the nervous system, including schizophrenia, depression, Alzheimer's disease, Parkinson's disease, and stroke.

The brain is still a mysterious organ. How it performs its myriad tasks is poorly understood. What is known is that the brain's development and function require the coordinated expression of nearly half of our genes. We can look forward to a time in the not-too-distant future when all of these genes will be identified, but this alone will tell us little about the mechanisms underlying the regulation of respiration or cardiac function, not to mention emotions, language, learning, or memory. To unravel these mechanisms, we have to learn the role of each gene product in specific cells of the brain. For this reason, we must continue to make a major investment in basic neuroscience. It is only by studying living nerve cells and intact animal or human subjects that molecular building blocks can be incorporated into blueprints depicting the organization and function of the brain. We need these blueprints in order to take advantage of the successes that molecular biologists have had in identifying genes responsible for inherited diseases of the nervous system.

Neuroscientists are rapidly isolating the molecules required for brain development, for the health and survival of brain cells, and for intercellular communication. How cells of the brain and different regions of the brain interact is becoming apparent. How visual information is encoded, words are spoken, and limbs are moved is growing clearer.



AN NIH SCIENTIST PREPARES RADIOACTIVELY LABELLED RNA SAMPLES. THIS TECHNIQUE CAN BE USED TO MEASURE THE EXPRESSION OF GENES IN THE BRAIN.

Intramural and extramural investment in neuroscience research must be expanded if we are to capitalize on these recent achievements. Growth of basic intellectual and physical resources — including the development of new technologies, data bases, model systems, and fundamental insights on the operation of the brain — will carry neuroscience and behavioral research forward toward new treatments.

Behavior and Health Across the Life Span: Biobehavioral Medicine

Health issues are influenced by the stages of the human life cycle. For example, adolescence is a period in which some health behavior problems emerge, including eating disorders, substance abuse, smoking, unsafe sexual practices, and the rise in rates of mental illnesses. The repercussions for society are enormous because unhealthy behaviors initiated during adolescence may result in higher mortality rates from addictive disorders, AIDS, heart disease, cancer, and other illnesses later on. Research must focus on the links between adolescent health and disease, beginning in childhood and spanning the entire life cycle. It is essential to clarify the biological, psychological, social, and environmental factors influencing behavior and health in order to develop coordinated public health strategies to solve these health issues.

Homicide, assault, child abuse, violence toward women, and suicide are among the most destructive forces in society. Homicide is the tenth leading cause of death in the U.S.; suicide is the eighth leading cause of death, and the third leading killer of the nation's youth. Mental illness is present in more than 90 percent of all suicides, and research has already shown important links between the abuse of alcohol and other drugs and the incidence of aggression, violence, and self-destructive behavior. Working with these and other leads, NIH-supported scientists will continue to explore the biological, environmental, and behavioral factors contributing to public health problems, and will develop appropriate interventions to prevent and treat these serious health concerns. In seeking to understand how healthy behaviors are established and maintained, it is important to consider how the individual, familial, social, and environmental contexts interact with relevant biological issues.

Biobehavioral medicine seeks to understand the relationship between behavior and physical illness in order to find ways to maximize healthy behaviors and minimize damaging ones. It also includes the development and application of both psychosocial and psychopharmacologic interventions to prevent and treat disease. Over the past several years, for example, growing evidence documents the communication between the immune system and the brain, and the production of neuropsychiatric symptoms in illnesses such as chronic fatigue syndrome, AIDS, some types of cancer, rheumatologic diseases, and endocrine and metabolic disorders. In addition, mental and addictive disorders are often found in people who have physical illnesses, providing evidence of ailments that co-occur (comorbidity). This may increase morbidity and mortality, but further studies are needed on the relationship of stress and illness to mental health and the effects of treating co-occurring mental and addictive disorders.

Major Goals: Behavior and Health

- *Evaluate the integration of the scientific and administrative functions of NIAAA, NIMH, and NIDA into NIH within 12 months of the merger*
- *Establish a mechanism within the Office of Disease Prevention to coordinate and promote trans-NIH efforts in behavioral medicine.*
- *Assure participation of behavioral scientists in the* Human Brain Initiative, *(see page 31).*
- *Expand and perfect the array of animal models of human neurological disease.*
- *Establish brain imaging centers as regional research resources.*
- *Establish a national patient registry of neurological disabilities and disorders.*

DESPITE DRAMATIC IMPROVEMENTS IN PUBLIC HEALTH AND MEDICAL CARE, EACH YEAR NEARLY 40,000 INFANTS DIE BEFORE REACHING THEIR FIRST BIRTHDAY. TO PRODUCE A NATION OF HEALTHY CHILDREN AND ADULTS, EACH BABY MUST BE "WELL BORN," WHICH MEANS THAT each infant will be wanted and will receive appropriate prenatal and postnatal care.

We have the knowledge to overcome many of the factors that contribute to high infant mortality, but we have not applied this knowledge effectively across society. Research thus far has produced only partial solutions for such problems as toxemia, premature labor, low birthweight, perinatal infections, respiratory distress syndrome, and sudden infant death syndrome (SIDS).

Many diseases have their origins in prenatal development, early childhood, and adolescence. One of NIH's priorities is to identify genetic markers and characteristics of infant and child health that can predict health problems later in life. Another priority is to develop preventive and therapeutic strategies that capitalize on this knowledge and allow intervention early in life.

New avenues of biomedical research have given us tools to explore the prenatal treatment of genetic disorders, to increase our knowledge of brain development and function, and to develop improved methods to screen infants for hearing or vision impairment. To promote healthy life, NIH is committed to these areas of research and others that promote the health of children and, ultimately, of the Nation's population as a whole. Research initiatives include:

- *Prenatal Care, Labor, and Delivery*
- *Fetal and Neonatal Disorders*
- *Childhood Antecedents of Adult Health and Disease*

Prenatal Care, Labor, and Delivery

The birth of a healthy baby depends in large measure on the care its mother receives before conception and during pregnancy. A relatively new concept in care is preconception evaluation and counseling, made possible by increased knowledge of genetics and the availability of genetic counseling, and improvements in the diagnosis and management of such maternal conditions as diabetes, hypertension, and infection.

Prenatal care affords an opportunity to intervene in such health-related behaviors as smoking, drug abuse, nutrition, and other factors that will affect the health of the mother and the developing fetus. This also is the best time to explore for genetic defects, intrauterine growth retardation, and other problems so the appropriate therapy, if available, can begin before or right after the baby is born.

Unfortunately, many women do not receive health care either before conception or during pregnancy. To address this concern, NIH is focusing on important behavioral research issues to determine how to encourage women to seek care during pregnancy, and continue health care visits throughout pregnancy, and how to ensure compliance with prescribed medical or health care regimens.

Premature labor is another problem being addressed. Currently, two-thirds of infant mortality occurs in low-birth-weight babies, often as a result of premature labor. Understanding the mechanisms responsible for sustaining pregnancy and preventing labor is a critical step in developing methods to stop the premature onset of labor and delivery.

Fetal and Neonatal Disorders

Fetal and neonatal disorders account for a growing percentage of infant deaths in the United States, with congenital abnormalities the leading cause. Some deaths have been linked to specific genetic defects, drugs, or environmental toxins, yet the etiology of the majority of cases remains unknown.

Two-thirds of all infant mortality takes place in the first month of life. Causes include respiratory distress syndrome, low birth weight, inadequate supply of blood and oxygen to vital organs (especially the brain), and neonatal infections. Sudden infant death syndrome (SIDS) is the leading cause of infant deaths after the first month of life.

A premature infant is monitored in a neonatal intensive care unit.

Intensified NIH-funded research efforts are needed to improve the techniques used to assess fetal well-being and detect fetal disorders; improve knowledge of the regulation of fetal growth; develop better noninvasive methods to assess placental function and fetal growth; develop optimal methods to provide nutritional, respiratory, and cardiovascular support to low birth weight babies and those suffering from manageable disorders, such as phenylketonuria; and elucidate the causes and underlying mechanisms responsible for SIDS, as well as develop prognostic and diagnostic tests to identify infants at risk.

Childhood Antecedents of Adult Health and Disease

The infant who develops free of major medical, dental, and/or behavioral problems has the best chance of becoming a healthy and productive child and adult. Screening and intervention in infancy may do more than improve current health; they may also reveal the antecedents of disease and health in later life. Screening for vision or hearing deficits in infants may permit earlier intervention that will result in improved adult health. Successful fetal-to-fetal cell transplantation to correct genetic defects heralds a new and exciting approach to preventing many other disorders. New understanding of the effects of child abuse will prevent later physical, emotional, and behavioral dysfunctions.

Since 80 percent of obese children become obese adults, we will try to develop genetic or metabolic screens to identify infants at risk for obesity later in life. Other nutritionally influenced conditions such as atherosclerotic cardiovascular disease, hypertension, certain forms of cancer, and non-insulin-dependent diabetes mellitus probably have their onset in childhood. These conditions may also benefit from more extensive assessment and nutritional intervention starting in infancy.

Major Goals: Childhood Health and Mortality

- *Integrate activity with the* Human Genome Project *to identify rapidly genes of potential applicability for prenatal/neonatal diagnosis and screening*
- *Develop new ways to assess fetal well-being and new fetal medical and surgical intervention strategies.*
- *Reduce the Nation's infant mortality rate through coordinated research strategies, including prevention strategies for SIDS and child abuse.*
- *Decrease the incidence of congenital anomalies including those associated with genetic defects, toxic exposure, and maternal disease, and improve intervention to repair or ameliorate these conditions.*
- *Establish a perinatal research branch in the District of Columbia and integrate the relevant activities of existing NIH research resources.*
- *Develop genetic, metabolic, and behvaioral screens to detect antecedents of adult disease, including mental illness.*

Reproductive Biology

The ability to procreate is fundamental to the survival of the species. As a result, reproductive disorders have a considerable impact on individuals and society, as do unplanned and unwanted pregnancies. Recent advances in molecular genetics, biochemistry, cell biology, and developmental models have catalyzed research on normal reproductive biology, development, and associated diseases. We have identified a number of genetic defects, infectious agents, and toxins that have adverse effects on reproduction. These advances have also underscored the need for new approaches to contraception, complicated pregnancy, infertility, and problems caused by such conditions as endometriosis and pelvic inflammatory disease.

Support for multidisciplinary efforts covering clinical, epidemiological, basic biomedical, and behavioral research will enable NIH to delineate reproductive and fetal disorders; identify the normal and abnormal molecular mechanisms of fertility regulation; and, ultimately, develop medical and behavioral interventions to prevent and control reproductive disorders, including sexually transmitted diseases.

NIH research initiatives in reproductive biology include:

- *Contraceptive Development and Sexually Transmitted Diseases*
- *Infertility*
- *Complications of Pregnancy*

Contraceptive Development and Sexually Transmitted Diseases

In 1923, the world's population was 1.9 billion; in 1985, it exceeded 5 billion. At the present rate, it will be more than 8 billion by the year 2023. However, population growth has slowed in countries with high rates of contraceptive use. For example, in 1987, 92 percent of women of reproductive age and at risk for pregnancy in this country used some form of contraception. For a majority of U.S. couples, birth spacing has become the norm. However, teenage pregnancy and sexually transmitted diseases (STDs) are still on the rise in major urban centers nationwide, and contraceptive use and development are inadequate around the world.

Many methods are too costly or complicated for worldwide application. In addition, existing options do not meet the needs of such people as very young women, women smokers over age 35, nursing mothers, and men or women who for medical reasons cannot use current methods. Research is needed to develop new, effective, inexpensive, and widely acceptable contraceptive options for both men and women, including natural methods of pregnancy prevention, suitable for global use.

A BLOOD SAMPLE FROM AN AIDS PATIENT IS PREPARED FOR TESTING.

One promising contraceptive approach interferes with meiosis, a process that occurs only in sperm and egg cells. A singular advantage of this approach is that no other cells would be affected. More intense study is needed on this and other promising methods of birth control. In addition, new technology must be accompanied by advances in our understanding of the behavioral factors that influence sexual activity and contraceptive use.

We must forcefully confront the "silent plague" of sexually transmitted diseases which threatens the health of women. Each year, 6 million women in the United States, half of them teenagers, acquire a sexually transmitted disease.

One of these diseases, human papillomavirus, has a strong correlation with cervical cancer. Two and one-half million women acquire chlamydial genital infections each year. Because of delays in diagnosis and treatment of chlamydia and gonorrhea, some 1 million women are treated for pelvic inflammatory disease each year. The consequences of pelvic inflammatory disease include infertility, tubal pregnancy, and chronic debilitating pain. Sexually transmitted diseases also put children at risk, with some 100,000 infants dying or suffering birth defects each year because of diseases transmitted during pregnancy or at birth.

INFERTILITY

Infertility affects between 35 and 70 million married couples around the world. In the United States alone, it is conservatively estimated that 2.3 million married couples are infertile and that about 4.9 million women have an impaired ability to have children. The role of sexually transmitted diseases as a cause of female infertility speaks to the need for better prevention strategies. These include barrier techniques that afford protection against sexually transmitted diseases as well as pregnancy.

Personal, familial, and societal costs aside, couples in this country spent more than $1 billion on infertility treatments in 1987. In the last 20 years, physician office visits for infertility services increased from 600,000 to 1,350,000 per year.

Unfortunately, up to half of the couples seeking fertility services will be unsuccessful in their attempts to conceive. Promoting reproductive health and overcoming infertility rest on our understanding of what controls fertilization and development, and the normal mechanisms involved in regulating reproductive and developmental processes.

Complications of Pregnancy

Spontaneous abortion and fetal injury affect a number of pregnancies. The causes of early pregnancy loss include genetic factors, anatomic anomalies, endocrine problems, immunologic factors, and infection.

Intrauterine infections are major contributors to unsuccessful pregnancies, and congenital infections due to cytomegalovirus, herpes simplex, syphilis, rubella, and toxoplasmosis can also produce profound fetal damage and clinical manifestations in infants. Fetal injuries can also be caused by environmental factors. Fetal alcohol syndrome is a prime example of a developmental disorder due to in utero exposure. Drug use during pregnancy can adversely affect the fetus as well.

Toxemia and high blood pressure affect more than 10 percent of pregnant women and contribute significantly to both maternal and infant mortality. Severe asthma in pregnant women increases the risk of preterm birth, intrauterine growth retardation, neonatal hypoxia, and neonatal mortality. Fetal and perinatal mortality is estimated to be between three and eight times higher in pregnancies of diabetic than nondiabetic mothers. However, the mechanisms by which asthma and diabetes exert adverse effects are not well understood.

Major Goals: Reproductive Biology

- *Increase the number and acceptability of safe, effective contraceptive options, including a reversible contraceptive vaccine and improved barrier techniques.*
- *Expand multisector collaborative contraceptive research and development programs involving government, university, and industry scientists.*
- *Establish research programs to reduce the incidence of infertility, unplanned pregnancies, and sexually transmitted diseases.*
- *Improve diagnosis and treatment of infertility.*

Disease Control and Prevention

Research toward disease prevention and control is central to the mission of the National Institutes of Health. All of the disease-oriented institutes have a stake in disease prevention. For example, NCI is launching a major study to determine whether the use of medical screening techniques and examinations for the early detection of prostate, lung, colorectal, and ovarian cancers can ultimately reduce the incidence of disease and death from these malignancies. This trial promises to provide scientists and physicians with important answers about the effectiveness of regular health care and early screening in the prevention of these life-threatening forms of cancer.

The Breast Cancer Prevention Trial, a precedent-setting effort in cancer prevention, was initiated by NCI to investigate the ability of tamoxifen, a hormonal agent, to prevent breast cancer in women at significant risk for developing the disease. The focus of this study is on decreasing the incidence of breast cancer, but tamoxifen's impact on cardiovascular disease and on osteoporotic bone fracture also will be assessed.

Integrated research programs on diet and fitness are vital in learning how to prevent disease and sustain good health. Although we have some understanding about the influence of diet and fitness on specific diseases, such as cancer, diabetes, osteoporosis, and atherosclerosis, more coordinated NIH research efforts are needed to enhance the promotion of general health.

A better understanding of the behavioral, biochemical, and genetic factors predisposing people to substance abuse and dependency is essential in designing effective, innovative prevention strategies and programs. People who abuse alcohol, tobacco, and drugs significantly increase their risk of premature death, not only from the toxic effects of these chemicals on the body, but also because they have a tendency to be subjected to other high-risk disease factors. Today, new studies are underway aimed at unraveling the role of both genes and the environment in the onset of alcoholism.

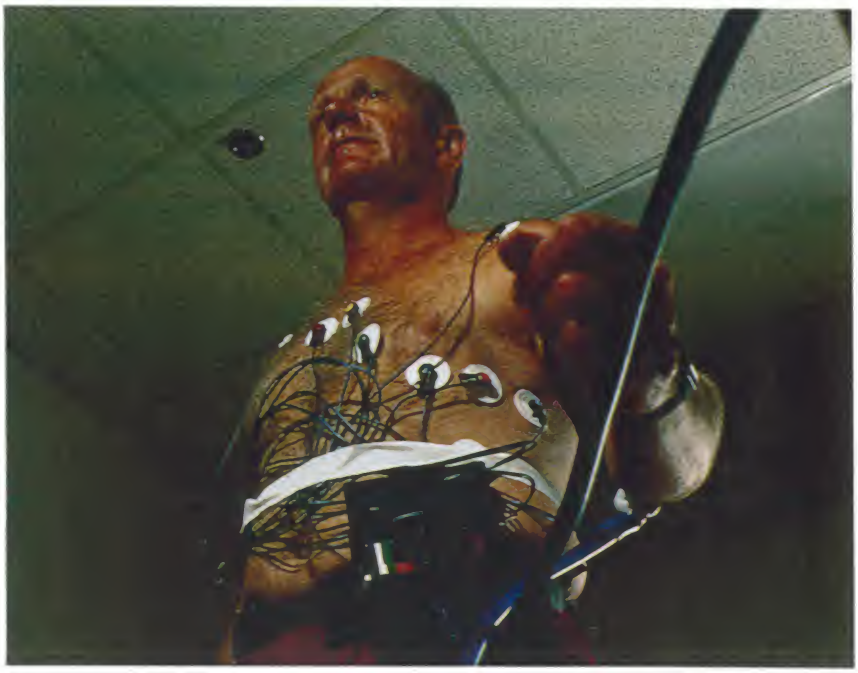
Investment today in disease prevention and control will reduce the human toll and economic burdens of disease tomorrow. Research on behavior now encompasses studies of ways of encouraging healthful behaviors for treating conditions such as hypertension, diabetes, glaucoma, and TB that require long-term compliance with a specific regimen. Other research initiatives of high priority for NIH include:

- *Promotion of General Health through Diet and Fitness*
- *Risk Factors, Early Detection, and Preventive Interventions*
- *Tobacco, Drugs, and Alcohol*

Promotion of General Health through Diet and Fitness

Diet and fitness are the building blocks of good health for people of all ages. Children and adolescents need a healthy diet and activity to ensure normal growth and development, and to lay the foundation for a healthy adult life. For adults, proper diet and exercise can reduce the likelihood of obesity and chronic diseases such as heart disease, hypertension, and cancer. By promoting good nutrition and fitness throughout the life span, NIH can make dramatic inroads in enhancing quality of life and independence for the Nation's rapidly growing population of older Americans.

More research is needed to sort out conflicts in dietary and exercise recommendations that are confusing to the American public. NIH seeks to establish a program of research on diet and fitness that spans the spectrum from basic nutritional science to research on how best to promote and achieve health and fitness recommendations for all Americans. New research efforts will evaluate the effects of eating patterns on blood pressure and on the appearance of biological markers of atherosclerosis. Particular attention will be given to the impact of increased fruit and vegetable consumption on the reduction of diet-related cancers and other diseases. Scientists also must expand their investigations into the effects of calcium and vitamin D intake and their interactions with hormonal factors in preventing osteoporosis. Fitness research must encompass studies that further examine and identify methods for maintaining and increasing long-term involvement in physical activity, particularly among children and the elderly.



A patient undergoes a "stress test" on a treadmill while electrodes monitor his cardiovascular system.

Risk Factors, Early Detection, and Preventive Interventions

Healthy diets, good sanitation, the widespread use of vaccines, community water fluoridation, and early diagnosis and treatment of health problems are among public health practices that have dramatically reduced the incidence of disease and extended the lives of countless individuals. Yet millions of people throughout the world continue to suffer from diseases and disabilities for which there are no known cures, including: atherosclerosis; certain cancers; chronic, degenerative kidney disease; diabetes; and many neurologic, sensory, and behavioral disorders, including conduct disorders in children and post-traumatic stress disorder in adults. Collectively, these illnesses cost billions of dollars in health care expenditures, represent major societal problems, and disproportionately burden the poor.

Current scientific knowledge and research tools are revolutionizing our understanding of the risks, causes, and progression of human disease and dysfunction. This expanding base of knowledge, particularly in molecular biology and human genetics, will lead to disease prevention and intervention strategies in the emerging discipline of molecular epidemiology. Our understanding of economic, demographic, social, and biological risks must converge to ensure that prevention and health education programs address the multiple influences on health and disease.

Tobacco, Drugs, and Alcohol

Abusers of alcohol and drugs are at increased risk of premature morbidity and mortality not only because of the direct toxic effects of these substances, but also because of concomitant high-risk lifestyle factors. Both active and passive exposure to tobacco smoke are associated with chronic lung disease, osteoporosis, and low birth weight.

Development of effective methods to prevent smoking, drug abuse, and alcoholism and to help addicted persons recover are important to improving the public health. A better understanding of the biochemical and genetic factors that predispose an individual to substance abuse and dependency is essential to the design of effective new preventive strategies.

Major Goals: Disease Control and Prevention

- *Conduct research to resolve conflicts and fill knowledge gaps in diet and fitness recommendations.*
- *Develop educational interventions for health care professionals, patients, and the public to promote general health.*
- *Develop innovative methods such as saliva tests to detect genetic susceptibility, risk exposure, or the early manifestations of preventable illness and disease.*
- *Coordinate across institutes studies on the effects of genetic and environmental factors, behavior, nutrition, and/or physical activity on preventing disease and substance abuse.*

TODAY FIVE OF THE 10 LEADING CAUSES OF DEATH FOR AMERICANS ARE DIET-RELATED, INCLUDING CORONARY HEART DISEASE, STROKE, DIABETES, AND SOME FORMS OF CANCER. ANOREXIA NERVOSA, AN EATING DISORDER THAT AFFECTS ONE PERCENT OF OUR adolescent girls and young women, also has a high mortality and morbidity rate. These statistics poignantly illustrate the need for scientists to investigate not only the relative significance of genetic and environmental factors contributing to disease, but also the long-term consequences of early nutritional experiences, as well as the effectiveness of disease prevention programs and strategies begun in childhood.

Bionutrition research employs molecular and genetic techniques to study the metabolic and behavioral consequences of food or nutrients, and explores the fundamental role nutrition plays in health maintenance and disease treatment. This research encompasses studies on nutrients at the cellular level, the metabolic function of nutrients in living organisms including humans, and studies on gene-nutrition-environment interactions.

The impact of the environment, from pollutants and stress to nutrients and radiation, figures prominently in understanding how these influences shape our genetic and biological destiny. Alterations in the nutrients an individual receives can provide protection against a genetic liability to disease or, conversely, can lead to disability, premature aging, or death.

Nutritional sciences are critical to the health of the entire population, yet this field has been sorely neglected. NIH intends to elevate the nutrition sciences as a priority through a focused research initiative in bionutrition. A research initiative in this area is:

- *NIH Bionutrition Initiative*

NIH BIONUTRITION INITIATIVE

The goal of the *NIH Bionutrition Initiative* is to apply the critical sciences and new technologies of basic biology to nutrition research questions. This initiative builds upon and interacts with research efforts underway in such areas as the environment, behavior, childhood health, reproductive biology, disease prevention, and the health of women and underserved populations. The *NIH Bionutrition Initiative* will increase NIH's commitment to nutrition research and training, enhancing its ability to provide timely, practical, comprehensive dietary guidance to Americans.

MAJOR GOALS: BIONUTRITION: STRENGTHENING THE SCIENCE BASE

- *Expand the science base underpinning our knowledge of human nutrition.*
- *Increase knowledge of nutritional interventions to prevent, cure, mitigate, or interrupt the progression of nutrition-related components of afflictions such as heart disease, cancer, diabetes, and AIDS.*
- *Use the science base to improve and refine health dietary guidance to achieve optimal health (see page 56).*
- *Establish an NIH Bionutrition Advisory Council as a focal point for training, research, and institutional collaborations under the* NIH Bionutrition Initiative.

Chronic and Recurrent Illness, Rehabilitation, and Aging

Americans now live longer and expect more from their later years than ever before. To meet these expectations, scientists must expand their knowledge of chronic and recurrent illness, rehabilitation, and aging. Research into the risk factors and causes of physical and mental illness will, in turn, translate into therapies and programs of benefit to millions of older Americans.

State-of-the-art assistive devices and effective rehabilitation techniques are enabling people with disabilities to become more productive members of society. Yet greater progress is needed to further reduce the years of disability, increase the years of healthy life, and decrease the costs to society and the individual of chronic and recurrent illnesses. The direct and indirect costs of chronic diseases in the United States are staggering. For example, it is estimated that the direct and indirect costs of cardiovascular disease exceed $100 billion annually, and approach $80 billion for Alzheimer's disease. Chronic conditions of mental illness, addictive disorders, and neurological diseases are responsible for over $300 billion in direct and indirect costs.

Developments in molecular and structural biology, indeed in all of the critical science fields, will advance research on chronic and recurrent illnesses, rehabilitation, and aging. The multifactor nature of chronic diseases makes NIH's goal of improving the lives of individuals with disease or disability a formidable challenge. Yet most researchers agree that functional decline is not inevitable. Through healthier lifestyles, careful application of promising medical therapies, and aggressive rehabilitation, a large segment of society can enjoy a better quality of life.

This area of research will require interdisciplinary efforts that bring together the best minds and resources from institutes across NIH and throughout its extramural community to address the complexities of these health problems. Major initiatives supported by NIH in this area of research include:

- *Reducing Dependency and Comorbidity from Chronic and Recurrent Illness*
- *Improving Rehabilitation Science and Technology*
- *Understanding Aging*

Reducing Dependency and Comorbidity from Chronic and Recurrent Illness

Chronic and recurrent illnesses exact a heavy human and financial toll on those afflicted, as well as on their caregivers and society. Directly or indirectly, these chronic illnesses — cancer, Alzheimer's disease, heart and vascular disease, diabetes, osteoporosis, arthritis, stroke and other neurological problems, mental illness, respiratory diseases, dental problems, gastrointestinal disorders, and allergies — affect every American. Many of them disproportionately strike women, minority groups, and other underserved populations. Others affect relatively small numbers of individuals, but there are over 5,000 of these "rare diseases" that collectively afflict as many as 20 million Americans.

Research into chronic illnesses poses complex challenges, involving intricate relationships among risk factors. Risk factors predisposing an individual to disease — physical, genetic, social, behavioral, or psychological — may occur many years before disease appears or may pose a risk only under certain circumstances. Scientists must take these many lifestyle factors into account, as well as consider the impact of physical and mental health on the onset and progression of disease.

Caring for people with chronic illnesses is another critical issue that NIH seeks to address. The presence of one or more chronic diseases is common in older people. Research to improve and reduce the burdens of care, particularly for long-term illnesses, is imperative. These studies, some in progress, must address such issues as new and evolving forms of care and social support systems for the chronically ill and their families. Of particular concern are AIDS, illnesses of the musculoskeletal system, schizophrenia, and dementias, which often leave individuals entirely dependent on family or an already overburdened health care system.

A PATIENT UNDERGOES A BRAIN SCAN USING MAGNETIC RESONANCE IMAGING OR "MRI"

Improving Rehabilitation Science and Technology

Between 35 and 43 million Americans have functional limitations as a result of disease or trauma. Nationwide, the incidence and general impact of disabilities are increasing, due to an aging population (there is a 50 percent chance that an individual over age 75 will develop a disability); a growing number of infants with congenital defects and impairments who are living longer; and an increasing number of disabled survivors of motor vehicle accidents, violence, and occupational injuries. As a result, rehabilitation research is becoming increasingly important to the Nation's health.

Rehabilitation medicine is a rapidly growing scientific field. Individuals in rehabilitation medicine are forming partnerships with basic and behavioral scientists to unravel the underlying complexities of human function and behavior, and applying this knowledge to reduce the consequences of disease and disability. This collaboration will result in new treatment approaches to minimize further functional decline, and lead to improvements in assistive devices, behavioral methods, and psychological counseling needed to help individuals with disabilities achieve a fuller measure of independence.

Understanding Aging

By the year 2000, the number of people age 85 or older is expected to double. In addition, there will be more than 65 million Americans age 65 or older by the year 2030. As never before, research on aging is vital, both to address the changing health problems of the elderly and to maximize their quality of life and independence.

Research has shown that the aging process varies greatly from person to person. A decline in health can often be attributed to external or self-induced factors, rather than factors intrinsic to aging. The notion that aging represents an inexorable decline into dependency and incompetence is being dispelled. New interventions, from exercise and better nutrition to changes in physical and social environment, are being tested to help older Americans remain healthy and active. The larger goal of geriatrics research is to decrease the incidence, severity, and rate of progression of disease in older people.

The most critical need in aging research and the one that holds the greatest promise is to strengthen vastly the fundamental science base. Research must sharpen its focus on the cellular and molecular events intrinsic to human aging. A detailed understanding of cell and tissue senescence is critical to any preventive strategies or interventions directed toward the elderly.

Major Goals: Chronic and Recurrent Illness, Rehabilitation, and Aging

- *Expand fundamental knowledge of the molecular and cellular biology of aging and age-linked cancers, vascular disease, mental illness, and neurological and immunologic decline in older people.*
- *Determine the role of genetic and immunological factors in the development of chronic and recurrent illness.*
- *Identify through population studies the genetic, biological, psychological, social, environmental, and economic factors associated with both development of, and survival and recovery from, chronic, recurrent, and age-related diseases.*
- *Develop improved methods of rehabilitation and long-term care.*
- *Develop sensitive, reliable indices of function and disability across the life span.*

Health of Women

Women live longer than men. However, they are more likely during their lifetime to experience illness or disability. The mental and physical health of American women has a direct bearing on the health of infants and children, and ultimately on the health of our Nation.

Some diseases are unique to women, or more prevalent among women, and many others involve different risk factors and interventions for women than for men. In addition to enhancing research on conditions that affect women, it is also critical to include greater numbers of women in the biomedical and behavioral studies and clinical trials conducted or funded by NIH.

NIH is committed to increasing knowledge about women's health, from conception through old age. This NIH-wide commitment is embodied in a partnership between the Office of Research on Women's Health and the institutes. NIH's goal is to ensure that gaps in knowledge related to women's health issues are addressed, and that a scientifically sound research agenda for women's health is set in motion now and for the future.

The objectives to be realized include: strengthening and enhancing research related to disease, disorders, and conditions affecting women; ensuring that women are appropriately represented in the biomedical and biobehavioral research studies supported by NIH; and developing opportunities and support for the recruitment, retention, and advancement of women in biomedical careers. Research initiatives supported by NIH in women's health include:

- *Women's Health Initiative and Women's Health Agenda*
- *Representation of Women in Biomedical Careers*

Women's Health Initiative and Women's Health Agenda

The *Women's Health Initiative*, a landmark disease prevention and health promotion trial, will address the three leading causes of death, disability, and frailty among postmenopausal women: cardiovascular disease, cancers, and osteoporosis. This pioneering study will provide practical information that women and their physicians can use to promote optimum health.

The initiative is being conducted in three parts: (1) a randomized, controlled trial that tests promising but unproven approaches to disease prevention, such as hormonal replacement therapy, a low-fat diet, and dietary supplements; (2) an observational study to identify the predictors of disease; and (3) an investigation of community approaches to develop healthy behaviors. This trans-NIH initiative brings together investigators from a majority of the institutes within NIH, the Office of Disease Prevention, Office of Research on Women's Health, and women's health advocates and community organizations throughout the United States to collaborate throughout the duration of the study. In all, about 160,000 women will participate in this 15-year study, which will prove invaluable in providing women and their health care providers much needed information about the benefits and risks of different approaches to disease prevention.

Through the *Women's Health Agenda*, NIH is pursuing the scientific knowledge to facilitate prevention strategies and clinical therapies to eradicate disease and improve quality of life for all women. To accomplish this goal, research is focusing on gaps in knowledge about women's health across the life span. This includes better understanding of how specific diseases and disorders affect women of different ages and racial backgrounds. Among those targeted for intensified research are infertility; contraception; sexually transmitted diseases, including HIV infection; mental diseases; cardiovascular diseases; connective tissue diseases, such as lupus and arthritis; breast cancer; and chronic pain.

Representation of Women in Biomedical Careers

To ensure that women are well represented in the biomedical sciences, their interest in and attraction to science must be nurtured and encouraged throughout all stages of their education, beginning in grade school and continuing as their careers evolve.

The recruitment of women into science training programs has increased steadily, with women well represented in graduate studies in medicine, dentistry, nursing, and basic and behavioral sciences. However, women are still underrepresented in leadership positions within these sciences. One of NIH's highest priorities is to recruit and advance greater numbers of talented women in biomedical careers, individuals capable of making significant contributions to their fields.

Major Goals: Health of Women

- *Fund more research grants to study diseases, disorders, and conditions affecting women of all races and ages.*
- *Pursue the* Women's Health Initiative.
- *Ensure the clinical inclusion of women in clinical trials at NIH.*
- *Expedite and enhance the dissemination of information resulting from women's health research to scientists, health care professionals, patients, and the public.*
- *Develop special training initiatives — especially at smaller colleges and minority institutions — to provide opportunities for young women to explore science as a possible career choice.*
- *Expand opportunities for women scientists and administrators, and advisors throughout the country, including at NIH.*

Health of Minorities and Underserved Populations

Minority groups represent less than one-quarter of the total U.S. population, yet they bear a disproportionate burden of the country's mortality rates stemming from disease and violence. Unfortunately, many minority Americans — African Americans, Hispanics, Asians, Pacific Islanders, Native Americans, and Alaskan Native citizens — are less likely than whites to live long and healthy lives. Likewise, underserved populations such as the physically and mentally disabled, impoverished Americans, the homeless, and migrant workers have the poorest overall health and, in most cases, no health insurance.

Minority and underserved populations also are underrepresented in biomedical research as participants in clinical research and investigations of diseases that affect these groups. Equally important, these groups are underrepresented as investigators in the biomedical sciences.

NIH recognizes the urgent need to close the health gaps between minorities and the remainder of the population, and to develop minority health and training programs in partnership with the minority communities. Research initiatives supported by NIH in this area include:

- *Minority Health Initiative*
- *Research Training for Underrepresented Minorities*

Minority Health Initiative

There is a wide difference in infant mortality rates between whites and blacks. In 1989, there were 8.2 deaths in 1,000 live births for whites, compared with 17.7 for blacks. Minority adolescents have higher rates of unintended pregnancy, sexually transmitted diseases, homicide, alcoholism, mental illness, and unintentional injury than their white counterparts. For many minority elderly, there is greater morbidity and mortality resulting from a higher incidence of chronic diseases than for whites.

To combat these serious problems, NIH has developed the *Minority Health Initiative* (see box, page 65). Its research efforts focus over the entire life span on health issues affecting the quality of life and life expectancy of minority groups. New research programs are being established to identify risk factors, prevention strategies, and treatments for the health problems of minority infants and youth, with particular emphasis on the causes and prevention of low birth weight, infant mortality, and sudden infant death syndrome; prenatal care to minority women; effective ways to increase immunization levels among minority children; and the impact of AIDS, drugs, tobacco, alcohol, and mental illness on minority individuals of all ages.

The Office of Minority Programs, created in 1990 to coordinate NIH-sponsored minority research and training programs, is responsible for implementing the *Minority Health Initiative*.

Health Initiatives

Infant Mortality

This initiative focuses on infant mortality and low birth weight infants through Washington, D.C.-based intervention trials to test improved methods of outreach aimed at early entry into prenatal care, social support, and behavioral change; studies also include perinatology research on nutrition, toxemia, premature labor and low birth weight.

Children's Health

This component focuses on injury-related morbidity, lead poisoning, asthma, learning disorders, and vision and speech impairment among minority children ages 1 through 9.

Adolescent Health

This project attempts to identify, implement, and evaluate behavorial interventions targeted for minority youths aged 10 to 24. The emphasis is on reduction of violence and the sequelae of sexual behavior. All of the projects are community- or school-based.

Young Adults

Projects focus on minority participation in periodic health screening and enhanced patient adherence to medical and behavioral treatment regimens. This component also includes studies on environmental health and tuberculois.

Older Adults

This component focuses on factors affecting the severity and progression of chronic diseases/conditions. Studies will examine the relationship of disease severity to specific types of functional impairment.

Training Initiatives

Regional Training and Research Centers

In collaboration with NSF, these regional centers involve a consortium of academic institutions — minority and majority. Education, research, and research training activities will be supported at each center site.

M.S./Ph.D. Bridge Program

Many minority students who earn M.S. degrees in the biological sciences do not continue on for a Ph.D. This program provides support and encouragement for those students to continue their education, by formally linking smaller M.S.-granting institutions with larger research universities.

2-Year/4-Year Bridge Program

A substantial percentage of minority high school graduates continue their education at 2-year institutions. This program provides incentives and support for students to continue their education in the biomedical sciences at a 4-year school after acquiring their 2-year degree.

Pre-College Intervention Program

In a partnership with NSF, the NIH Office of Minority Programs will support middle school and high school academic enrichment programs in the biomedical sciences (e.g. biology, chemistry, etc.).

International Research Program

In partnership with the Fogarty International Center, this program provides for international research experiences for undergraduate, graduate, and postdoctoral minority students and faculty.

Evaluation of NIH Minority Training

The Office of Minority Programs will collect data from each of the institutes to determine the level of support for minority training programs at NIH, and also the impact of those programs in terms of the number of students and researchers in the "pipeline" who are supported by NIH funds.

Research Training for Underrepresented Minorities

Minority Americans are underrepresented in the sciences. This is true in the private sector, on university campuses, and in secondary school programs. The United States' best hope to secure its economic competitiveness in the world, provide adequate health care for all its citizens, and improve society's general welfare is to diversify its workforce. Achieving these goals requires greater access to higher education for minority students.

By the year 2000, 68 percent of those entering the Nation's workforce will be minorities and women — groups traditionally underrepresented in the biological sciences. In 1990, 4,779 doctorates were awarded in the United States in the life sciences, but only 128 (3 percent) of those doctoral degrees went to Hispanics, 91 (2 percent) to blacks, and 8 to Native Americans.

NIH recognizes that the problem begins at the elementary grade level and continues through graduate school. Thus, strategies must focus on the entire educational pipeline — from early schooling through graduate school and beyond. The Office of Minority Programs is augmenting institute activities to increase the number of minority biomedical scientists through a range of academic enrichment and research training programs specifically targeted to minority students.

For example, NIH is promoting special programs at colleges and universities offering graduate and doctoral programs that will assist minority students in making a smooth transition from a master of science degree program into a Ph.D. program. NIH also is collaborating with the National Science Foundation to support several academic enrichment programs for pre-college and undergraduate students. Often precollege programs are instrumental in encouraging minority students to pursue science in college by affording them the opportunity to receive hands-on laboratory experience and to explore career opportunities and challenges in the biomedical and behavioral sciences.

By focusing greater attention and resources on the entire educational pipeline, NIH's Office of Minority Programs strives to encourage greater numbers of minority men and women to continue their science education and pursue careers in the biomedical sciences.

Major Goals: Health of Minorities and Underserved Populations

- *Pursue the* Minority Health Initiative.
- *Strengthen partnerships between NIH and the minority community to promote general health and disease prevention. This is crucial for minority participation in clinical trials and the success of the* Minority Health Initiative.
- *Foster and increase minority participation in clinical trials and population-based studies across NIH.*
- *Improve instructional and enrichment activities in science for minority students and teachers.*
- *Increase recruitment and retention of minority biomedical scientists and administrators, intramurally and extramurally.*

Intellectual Capital

The empires of the future are the empires of the mind.

— *Winston Churchill, British statesman*

If you think education is expensive, try ignorance.

— *Derek Bok, American educator*

America is strong because of the pioneering spirit, innovation, and individual achievement of its people. These qualities find no greater expression than in science. A robust and diverse talent base is especially vital to the competitiveness of the present and future of the biomedical research enterprise and its associated industries, and also is key to achieving the Nation's education goals. Thus, it is of primary strategic importance to maintain and enhance the talent pool in science, including strengthening research training and career development and ensuring the recruitment and retention of underrepresented groups into science.

Development of the Scientific Talent Base

People, the source of all biomedical ideas and inspiration, are indisputably our most precious resource. Maintaining a cadre of talented individuals in the biological sciences is essential to improve the health of the public and sustain the economic prosperity of our Nation.

NIH's role in nurturing the United States' scientific talent base is played out through a variety of innovative programs designed to support students from high school through postdoctoral training. It is during this stage that many students make a commitment to research careers. NIH's goal to bolster the Nation's intellectual capital includes attracting more women and members of minority groups to careers in science to ensure that research issues germane to these groups are addressed.

The changing frontiers of science demand a broad understanding of scientific principles and practices, and of the implications of current discoveries on future research opportunities. To meet this challenge, NIH-supported research training increasingly spans many disciplines and academic departments. NIH must address current shortages of research personnel in fundamental research areas such as structural biology and rational drug design, and in clinical research. The initiatives NIH has implemented to achieve this goal include:

- *Support for Research Training and Career Development*
- *Research Flexibility*

Support for Research Training and Career Development

As NIH has come under growing fiscal constraints, the training and career development component of our budget has been disproportionately affected. To address the Nation's human resource needs and expand the base of its scientific talent — in both basic science and clinical research — NIH is committed to promoting career programs geared to sustain and strengthen our intellectual capital. It has reaffirmed or instituted a number of innovative programs that, as a continuum of support, are crucial to the intellectual base of the biomedical research enterprise:

National Research Service Award (NRSA) Research Training — NIH supports predoctoral and postdoctoral research training using research training grants to institutions and fellowship awards to individuals. These awards are designed to assist the development of graduate students and individuals in postdoctoral (M.D. and Ph.D.) training into independent and productive biomedical and behavioral scientists.

A CLINICAL PATHOLOGIST SCREENS AGAR PLATES FOR POTENTIALLY PATHOGENIC ORGANISMS.

NIH Research Career Awards — NIH uses research career awards to support mentored research experiences for individuals with clinical-professional degrees such as the M.D. and the D.D.S.

FIRST Awards — FIRST Awards support an investigator's first independent research project, thus promoting the transition to an independent career in biomedical research. This program has become so competitive that recipients are often well into their research career before they can mount a successful application.

James A. Shannon Awards — This awards program, created in 1991, supports research projects that just missed NIH's funding cutoff. The majority go to young, promising investigators or experienced scientists who need bridge funding to continue their work.

Junior RO1 — This new program will focus primarily on young investigators who are completing their postdoctoral training. It will serve as a transition mechanism to independent research, enabling investigators to obtain preliminary data and information prior to applying for an RO1.

High Risk/Innovative Research — This research program will support research that is considered high risk and whose exploration has the potential for high payoff. Investigators would submit an abbreviated application, stressing the novel aspects of the research. This award for $50,000 direct cost per year for two years will be nonrenewable and funded from an institute set-aside of funds.

Administrative Supplements — NIH has established a program of administrative supplements to existing research grants and cooperative agreements as a means of recruiting minorities at the high school, college, graduate, postdoctoral, and investigator levels.

Intramural Research Career Development — Intramural NIH supports the full spectrum of career development programs in basic and clinical research at the Bethesda campus.

Traditionally, Congress requests that the National Academy of Sciences (NAS) perform a quadrennial manpower needs assessment for research training. In 1993, for the first time, NIH asked NAS to conduct a "zero-based" study on the efficiency and efficacy of existing training programs and to develop recommendations for resources for the future.

Research Flexibility

Research is unpredictable. Serendipity has played a role in some of the most important scientific discoveries of our time. That is why creativity and flexibility — elements essential for nurturing innovation — must be safeguarded in biomedical research. For example, an investigator exploring the efficacy of a drug in disease treatment may unexpectedly discover a new, even more promising application. However, changing directions for this investigator may require more resources than were provided in the original grant. Research flexibility means having the capacity to capitalize on such opportunities, as well as to be responsive to promising young investigators.

Currently, the highly competitive nature of the NIH grant system makes it difficult for young investigators to compete successfully for traditional project grants until they have proven themselves, a "Catch-22" that compromises our ability to tap this pool of talent for exciting, innovative research. The James A. Shannon Awards, established in 1991, are an example of NIH's efforts to create flexible grant mechanisms that provide support to promising young investigators who fall just short of the funding cutoff. Indeed, retaining current investigators is as crucial as recruiting new scientific talent.

NIH also recognizes the need to provide greater flexibility and stability to its awardee institutions in other situations. Whether it be lapses in project funding, equipment failures, or facility problems that arise without warning, NIH should have the capability to respond in a timely manner.

Major Goals: Development of the Scientific Talent Base

- *Develop more reliable techniques for assessing the supply of and demand for researchers, based on the findings of the NAS study.*
- *Attract a greater number of young scientists as principal investigators in both basic and clinical research*
- *Improve representation of women and minorities pursuing basic science and clinical research careers in biomedicine.*
- *Explore and evaluate novel and innovative career development mechanisms, such as Shannon Awards and Junior RO1s.*
- *Expedite the approval of competitive grant submissions by young investigators.*
- *Implement a system of re-entry grants for older investigators, particularly women.*

The failure to attract young students to careers in science will lead to an inadequate supply of trained scientists to meet the Nation's needs by the year 2000. We must begin now to prepare the next generation of life scientists well before they enter college. This has led the NIH to expand its educational programs aimed at elementary through high school students, as well as at teachers and the general public.

Public understanding of science also is critical to the NIH and its capacity to fulfill its mission. The public, social, and economic health of the United States depends increasingly on people who understand science, and the use of science and technology in society. Yet recent studies indicate that more than 90 percent of U.S. adults are scientifically illiterate.

Major initiatives supported by NIH to address these issues include:

- *Teacher Preparation/Enrichment and Student Incentives*
- *Public Understanding of Science*

Teacher Preparation/ Enrichment and Student Incentives

Teachers are instrumental in cultivating or discouraging students' interest in science. In that regard, NIH is pioneering new programs to give precollegiate life science instructors research experience during their undergraduate years, and opportunities to interact with investigators during their teaching careers. These experiences are designed to enhance the teachers' own scientific literacy, to expose them to cutting-edge research and technologies, and to strengthen their teaching skills and increase their enthusiasm for teaching science.

A steady flow of new science students is needed to increase the number interested in becoming life science teachers or biomedical scientists. NIH recognizes the working scientist as its most valuable resource in keeping students interested in science throughout their education. As mentor and role model, the scientist can encourage students to pursue careers in the sciences. NIH's Science Education Partnership Award Program has expanded interaction between NIH and the education community through science education pilot studies such as adopt-a-school alliances and information-sharing among elementary school educators and groups of NIH scientists. At the high school level, the Science Training Education Award Partnership (STEAP) Program fosters research training for science teachers in order to create a corps of master science teachers in local school systems. In combination with other programs, STEAP also brings students into basic research laboratories for hands-on experience and exposure to research methods and techniques.

NIH plans to continue its active role in facilitating interagency cooperation in pursuit of its life sciences education goals. For example, efforts are underway to link the NIH precollege science education program to the HHS Head Start program. Major efforts will also concentrate on stimulating interest and participation from intramural and extramural constituencies.

Public Understanding of Science

NIH gives high priority to promoting public scientific literacy. Without an understanding of science and the ability to apply basic scientific principles to everyday life, the public is ill-equipped to make difficult political and ethical decisions involving biomedical issues and emerging technologies.

To enhance the public's understanding of science, NIH is forming educational partnerships with universities, industry, and State Science Coordinators nationwide. NIH is playing a leadership role in these partnerships by developing a coordinated plan for science literacy involving all agencies of the Federal government. Programs slated for development include a pilot Evening Scholars Program, to give the public a better appreciation of NIH investigators and their important work; a coordinated, nationwide NIH Public Science Literacy Campaign; and the inclusion of more science information in educational materials distributed by the institutes.

Major Goals: Life Sciences Education and Public Understanding of Science

- *Provide new training opportunities for teachers to update their knowledge, skills, and abilities in science.*
- *Strengthen and expand the use of innovative and hands-on learning experiences in classrooms by teachers.*
- *Significantly increase the number of students participating in NIH programs, pursuing extracurricular science activities, and receiving awards or educational fellowships for scientific achievement.*
- *Establish aggressive public education programs to increase the number of scientifically literate citizens.*
- *Coordinate efforts across Federal agencies to develop a science literacy campaign.*

Professional Standards of Scientific Research

THE HIGHEST STANDARDS OF INTEGRITY AND OBJECTIVITY ARE PARAMOUNT FOR THE CONDUCT AND REPORTING OF RESEARCH BY THE SCIENTIFIC COMMUNITY. NIH, AS A STEWARD OF PUBLIC FUNDS AND DEPENDENT ON PUBLIC TRUST, MUST WORK WITH INVESTIGATORS AND institutions across the Nation to ensure that the highest standards are established and sustained.

Historically, cases of fraud and misrepresentation in science have been rare. However, in recent years, there has been an increasing visibility regarding matters of scientific misconduct. The magnitude and importance of today's science demand that institutions, faculty, and students share a common ethos regarding acceptable standards of science, and how those standards can be ensured.

In addition to presenting their data accurately and fairly, scientists must also respect the rights of human subjects and ensure the welfare of animals used in research, take precautions if the research is hazardous, and share the results with others honestly, completely, and promptly.

Working in cooperation with institutions, professionals, and academic societies, NIH will develop policies and guidelines for such issues as conflict of interest and standards of scientific conduct.

Major Goals: Professional Standards of Scientific Research

- *Expand the number of academic institutions with a curriculum in scientific integrity to address such issues as conflicts of interest and the honest, accurate reporting of research data.*
- *Promote high standards of scientific and professional conduct for the NIH intramural research program.*
- *Foster consensus building within all segments of the scientific community, utilizing NIH advisory and peer review committees; and develop informational programs to communicate the resulting standards to the general public.*
- *Finalize NIH Guidelines on Conflict of Interest.*

Strategic Objective 4: Research Capacity

If you build it, [they] will come.

— William Kinsella, *Shoeless Joe* ("Field of Dreams")

The United States succeeds in science and technology today because of its sustained, long-term investment in nationwide research capacity. Built on a foundation of public-private partnerships, NIH invests not only in its own facilities but also in a diverse network of extramural institutions. Conducting research that advances critical science and technology and addresses the Nation's critical health needs, requires physical and methodological infrastructures that include instrumentation, research resources, support services, laboratory facilities, and enabling technologies.

NIH has five organizational components focusing specifically on these infrastructure and support needs:

Division of Research Grants (DRG)(1946)

DRG is the gateway to NIH funding for all extramural research and training projects. One of its most important responsibilities is to administer peer review, a system of Study Sections and Special Review Groups that evaluate grant applications for scientific and technical merit. DRG also operates several computer-based data systems for managing, tracking, and evaluating research funding.

Warren Grant Magnuson Clinical Center (CC)(1953)

The Clinical Center is NIH's 500-bed clinical research hospital, handling over 9,000 inpatient admissions and 160,000 outpatient visits each year. Specially designed for clinical research, this hospital enables scientists to monitor closely the care of patients involved in clinical trials. As a result, the Clinical Center has been the proving ground for many pioneering developments, most recently the first trials of human gene therapy for certain cancers and an inherited disease.

Division of Computer Research and Technology (DCRT)(1954)

The Division serves NIH by developing computer-based information management systems for laboratory, clinical, and administrative applications. Image-processing technologies developed by DCRT have contributed to progress in structural biology and the analysis of protein sequences in human genome research. DCRT has also pioneered the development of biomedical applications of high-performance computing. Future efforts will include continuing the implementation of computationally intensive methods of drug and vaccine design and protein structure analysis and enhancing the computational, networking, database, and informatics capabilities throughout NIH.

National Center for Research Resources (NCRR)(1956)

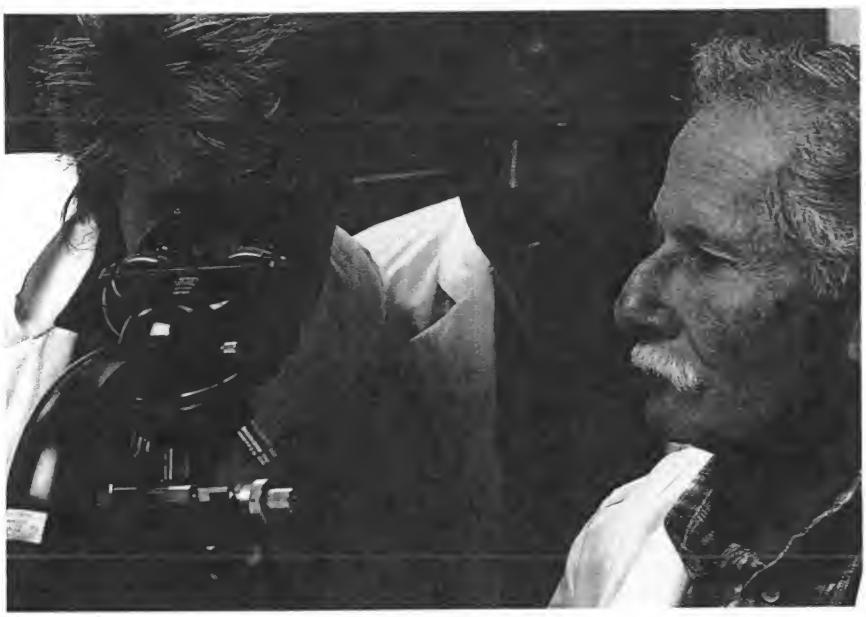
NCRR develops and supports critical research technologies and shared resources that underpin research to maintain and improve the health of our Nation's citizens. NCRR supports sophisticated instrumentation and technology, animal models for studies of human disease, clinical research environments, and increasing research capacity for underrepresented groups. NCRR supported the development of the first laboratory computer, artificial intelligence applications for medicine, and the primate model of AIDS. Current and future programs emphasize an array of bioengineering and biotechnologies, including marine biotechnology, computer-aided drug design, and structural biology, as well as gene-derived therapies and vaccine development.

National Library of Medicine (NLM)(1956)

NLM multiplies the value and impact of NIH research findings by making them widely available to the Nation's physicians, research scientists, and other health care professionals. Computer searches using NLM information resources have already contributed to patient care and to breakthrough discoveries on the molecular basis of cancer, inherited diseases, and the immune system. Future efforts will emphasize connectivity to high-speed computer networks for research and patient care.

Intramural NIH: Revitalizing A National Resource

The NIH intramural research program is at once a paradigm for the conduct of innovative, risk-taking science, a hub of coordination, and a proving ground for the entire biomedical research enterprise. Approximately 11 percent of the total NIH budget supports this critical mass of talented scientists and clinicians working in a unique environment where basic research labs stand side by side with patient care units. The creative freedom provided to thousands of researchers has proven to be uniquely efficient in fostering and catalyzing discovery and productivity. Laboratories worldwide draw ideas and leadership from these programs.



Two post-doctoral fellows work alongside an NIH scientist as participants in the Intramural Research Training Award (IRTA) program.

The program's excellence is reflected in Nobel prize-winning work, including the unraveling of the genetic code, the elucidation of protein folding, and the discovery of new neurotransmitters and a class of slow viruses that cause certain neurological diseases. Intramural research has provided fundamental insights leading to the development of monoclonal antibodies, the concept of oncogenes, recombinant DNA techniques, and vaccines against meningitis, pneumonia, pertussis, and other bacterial infections. Clinical achievements include pioneering gene therapy, development of the HIV-1 blood test, use of AZT, ddI, and ddC as treatments for AIDS, and curative chemotherapy for certain leukemias and lymphomas.

Some 50,000 scientists have trained in our laboratories and clinics, and they now form a core of scientific leadership around the world. Many of these alumni comment that they did their most innovative work as NIH intramural scientists. This reflects the elements of scientific freedom, resource security, and intense interaction among colleagues from different disciplines that characterize intramural NIH.

The strong interface between basic and applied science allows us to push aggressively from basic discovery to application and development. The intramural research program is unmatched in large part because of the Warren Grant Magnuson Clinical Center, the world's largest hospital devoted solely to clinical research.

Although the intramural research program remains among the most productive and prestigious biomedical research institutions in the world, it has experienced serious problems over the past decade, including barriers to recruitment and retention of senior scientists, regulatory burdens, and declining infrastructure. These problems have a negative impact on the morale of intramural scientists.

Through the strategic planning process, we have identified the intramural research program as among NIH's highest priorities in support of its missions. Accordingly, we are taking determined action to foster a renaissance in our intramural program. We have called upon our most creative and energetic scientists to identify needed directions and actions, as articulated in the Report of the Task Force on the Intramural Program, the Women's Task Force report, and the NIH Intramural Career Development Initiative. New, visionary leadership has arisen from the ranks of the intramural scientists. And we are beginning to reverse the brain drain with the recruitment of a world-class physician-scientist, with his staff, to head the *Human Genome Program* and build a new multidisciplinary intramural research program in human genetics. This renaissance will continue with the development of a Master Plan for the NIH campus of the future.

Major Goals:
Intramural NIH: Revitalizing a National Resource

- *Assure a critical mass of scientific talent and a stable, nurturing environment to conduct risk-taking basic research of the highest originality, poised to respond swiftly to unanticipated research opportunities and emerging public health crises.*
- *Maintain quality by the external peer review of scientific accomplishments, using the outcome to determine scientist retention, promotion, and resource allocation.*
- *Sustain the depth and quality of fundamental science with emphasis on areas of promise and their therapeutic translation, including human genetics, molecular and cell biology, structural biology, and gene therapy.*
- *Foster teamwork between basic and clinical scientists in order to rapidly convert the findings of basic research into innovative clinical strategies and therapeutics. Encourage, as appropriate, partnerships with academia and industry.*
- *Improve recruitment and retention of scientific leaders by implementing the findings of the Task Force on the Intramural Program, the Women's Task Force report, and the Career Development Initiative.*
- *Complete the NIH Master Plan and develop an implementation plan. Identify and secure the core technologies necessary to provide preeminent research capabilities.*

Clinical Research

There is an urgent need for scientists oriented toward the needs of patients who will strengthen America's clinical research capacity. Clinical research is vital to our biomedical research enterprise because it is the bridge between the laboratory bench and the patient, translating our fundamental knowledge and understanding of human biology and disease into clinical therapies to detect, treat, prevent, and cure disease.

The accelerating pace of discovery in the biological sciences is far outstripping the scientific community's capacity to translate laboratory advances into applications that benefit the public. In order to take full advantage of this expanding fundamental base of knowledge, NIH must significantly increase its investment in clinical research. However, the barriers to clinical research involve not only training and funding limitations, but also limitations on the actual conduct and design of research.

Major Goals: Clinical Research

- *Design more effective and attractive training programs for clinical investigators to ensure that essential clinical research technologies — for example, biostatistics, epidemiology, study design (including clinical trials), bioethics, basic laboratory techniques, human subjects protection — are included in the curriculum.*
- *Foster a multidisciplinary approach to clinical research to ensure that the striking, recent advances in molecular biology, biotechnology, immunology, and the neurosciences are translated to patients.*
- *Develop needed animal models of human disease through cost effective mechanisms that allow access to a wide array of investigators.*
- *Develop new clinical research biostatistical tools along with improved outcome measures and clinical end points to enhance the quality of clinical trials and to reduce their cost.*
- *Establish regional and national resources to offer professional guidance in study design, implementation, and data analyses for a wide array of investigations.*

Research Resources, Facilities, and Instrumentation

The rapid pace of scientific discovery witnessed in the past 25 years owes much to investigators having access to state-of-the-art equipment, facilities, and technologies central to the conduct of research. The National Institutes of Health figures prominently in ensuring that intramural and extramural scientists have access to these resources, and in developing innovative cost and resource sharing mechanisms to make finite public resources go much further. These shared resources are key to the success of all NIH strategic objectives. Major initiatives supported by NIH in this area include:

- *Shared Resources*
- *Construction/Renewal of Facilities*
- *Enabling Technologies/Instrumentation*
- *Computational Biology*

Shared Resources

Shared resources — core facilities, tissue and cell banks, animal research centers — provide the most cost-effective way to support complex research, while speeding the translation of basic science ideas into patient care and cures. In this area, NIH will assess and support needed national, regional, or institutional shared resources, as well as monitor an institution's use of existing resources to establish integrated research collaborations among investigators.

NIH currently supports a wide variety of shared resources that provide critical biomaterials to the research community. These include a facility that acquires and distributes microorganisms, including viruses, bacteria, fungi, and yeast; a center that collects and distributes over 1,600 strains of nematodes; a genetic stock center that contains over 1,000 strains of a yeast; a repository that collects and provides cloned genes, DNA probes, and human chromosome libraries; a repository that stores and distributes human cell lines from individuals with genetic disorders; and a number of resources that provide specialized strains of animals.

A typical NIH intramural laboratory.

Construction/Renewal of Facilities

Over the past decade, NIH has worked with the National Science Foundation to assess the need for new and refurbished research facilities nationwide. Among the disconcerting findings of their study are (1) that a majority of facilities do not meet strict regulatory and environmental standards, (2) that many have deteriorated so badly they must be replaced, and (3) that construction costs to meet changing technological and regulatory requirements have skyrocketed.

The scientific initiatives outlined in this plan impose additional requirements for research facilities in such areas as molecular medicine and biotechnology. In the absence of Federal monies beyond those provided by indirect cost reimbursement, many institutions, particularly minority and emerging institutions, cannot generate sufficient funding from other sources to adapt existing space or add new space for biomedical research.

Enabling Technologies/ Instrumentation

Nuclear magnetic resonance spectroscopy and X-ray crystallography are among many technologies increasingly important to our understanding of the molecular basis of human disease and health. These and other "enabling technologies" are essential to research efforts across many disciplines of science. Yet many can be provided only through national or regional resource centers.

For example, progress in molecular medicine has accelerated with the development of sophisticated tools to isolate, purify, and characterize the structure of biologically important molecules. Equipment critical to this type of research, such as synchrotron X-ray sources — powerful tools for determining molecular structure — must be available to scientists. NIH has helped make this possible through synchrotron facilities supported by the National Center for Research Resources, the Department of Energy, and the National Science Foundation.

Likewise, enabling technologies that include organisms and animal models allow scientists to study both simple and complex biological activity. NIH recognizes the importance of these models in developing new scientific methods and hypotheses, and in understanding different biological systems and their subtle or profound connections to human life.

Computational Biology

Mapping the human genome. Predicting the structure and function of 100,000 new proteins. Designing drugs based on the structure of the target. Analyzing complex population-based studies. These biomedical challenges hinge on advanced computer technology and scientists with a high level of proficiency and sophistication in the use of computing.

The scientific promise of molecular medicine, biotechnology, structural biology — and almost every existing and emerging field of science — cannot be realized without high-performance computer and communications systems. In addition, scientists working around the globe increasingly depend on a powerful computer network to collaborate using electronic mail to transmit important data, and to access biomedical databases throughout the United States and the world.

NIH is also participating in the High-Performance Computing and Communications Initiative (HPCC), a multi-agency, multi-year Federal effort to strengthen our Nation's computing resources for research. Other participants include the Departments of Energy and Defense, the National Science Foundation, and the National Aeronautics and Space Administration. NIH and its nationwide community of researchers will benefit enormously if HPCC results in the development of new computer technologies and biomedical applications that provide new insights into previously unapproachable research and clinical problems.

Major Goals: Research Resources, Facilities, and Instrumentation

- *Continue to stress the need to renew the Nation's research capacity by renovating and constructing research facilities to meet the technological and space requirements of 21st century biomedical science and strive to define more precisely the appropriate Federal and NIH roles in this renewal.*
- *Facilitate the biomedical research community's access to federally owned technologies and instrumentation, such as high-performance computing resources, synchrotron, and X-ray crystallography.*
- *Explore the development of national and regional centers to house enabling technologies and resources, such as P-4 containment facilities, and ensure optimal access to existing resource centers.*
- *Substantially increase the number of new scientific collaborations among NIH-supported research groups enabled by national and international computer networks.*
- *Utilize the newest generations of massively parallel, scalable supercomputers to attack the previously intractable "grand challenge" problems of biomedicine, such as drug and vaccine design, predicting protein structure, and homology modeling.*
- *Promote the use of high-performance computers and high-speed networking to improve the efficiency, performance, and cost-effectiveness of biomedical research and delivery of health care.*

Stewardship of Public Resources

I believe that every right implies a responsibility; every opportunity, an obligation; every possession, a duty.

— *John D. Rockefeller, American industrialist and philanthropist*

NIH represents a $10 billion investment by Americans based upon the expectation of a substantial return to themselves and their loved ones. That investment will continue only as long as the public is confident that it is managed wisely. Stewardship of public funds entails supporting outstanding scientists who advance the enterprise through meritorious research performed in the interest of the public. The key to achieving responsible stewardship is the presence of innovative and quality managers and quality management systems. Above all, stewardship demands integrity and fairness in the conduct of our business.

Economic Analysis and Budget Policy

In an era of finite public resources and greater societal demand for health care, the National Institutes of Health must develop sound, effective budget strategies to compete effectively for resources. Once appropriated, resources must be allocated efficiently and fairly, and to areas most likely to reduce the incidence of disease and improve human health.

NIH's budget has not kept pace with the expanding opportunities and advances in biomedical research. Historically, growth in NIH's budget has been significant. Between 1989 and 1993, however, NIH funding grew at approximately the same rate as total domestic discretionary funding, and at rates lower than those for other Federal science agencies.

Several factors may contribute to this decline. Much of the earlier growth in the NIH budget was the result of congressional backing, but current budget ceilings significantly preclude increases to the President's Budget. At the same time, other Federal science agencies have benefited recently because they were designated as presidential priorities. Furthermore, at every phase of the budget process, NIH does not compete with science agencies whose budgets are seen as investments in the future; it competes instead with human service programs that demand immediate attention. As long as health care costs rise significantly faster than the rate of inflation, and until a priority is established on investment, NIH will be at a disadvantage. Finally, many NIH-sponsored research programs are not well understood by the media and public. Many people have yet to appreciate fully that improvements in public health and the associated reductions in health care costs result from investment in biomedical research.

A MOLECULAR BIOLOGIST ASPIRATES A GEL SAMPLE FOR ELECTROPHORESIS.

NIH budget development must flow from the investment priorities established by an ongoing NIH strategic planning process, rather than focusing (as it has in the past) on mechanisms of support. This new budget strategy must acknowledge that the ultimate solution to many health care financing issues lies with the knowledge derived from fundamental research. For example, with 40 percent of Medicaid's budget paying for nursing home costs, the need for solutions to chronic, debilitating conditions such as Alzheimer's disease, stroke, mental illness, and osteoporosis is compelling. A stronger investment now in finding solutions for those diseases would pay dividends many times over in future savings on nursing home costs.

At the same time, this process must take into account the fact that basic research into complex diseases must be sustained for years, even decades, before clinical applications can be developed. Accordingly, NIH is committed to long-term budget development and economic analyses that articulate priorities in biomedical research and promote public understanding of the economic and human value of NIH-supported research.

Major Goals: Economic Analysis and Budget Policy

- *Develop and present the NIH budget based on the priorities established in the NIH strategic planning process, which articulate the benefits of investment in the future.*
- *Refine further the models that allow more sophisticated analyses of the long-term applications of budget decisions. In doing so, the practicality of measurable indicators such as improved health and quality of life as factors influencing resource allocation should be analyzed.*
- *Conduct a review every two years to assess the implementation and success of the ongoing strategic planning process as a means for guiding resource allocation.*

Technology Transfer

The National Institutes of Health has an important mandate to transfer the fruits of biomedical research to the private sector to facilitate the development of drugs and other products of immediate benefit to human health. This mandate includes the licensing of intellectual property rights and information sharing to ensure that research advances find rapid, appropriate application in medical practice.

To promote technology transfer, Congress enacted legislation in the early 1980s that permitted government grantees and contractors to retain title to federally funded inventions. It also encouraged universities to collaborate with industry to further promote research, to develop useful products, and to license those inventions to industry. The Federal Technology Transfer Act of 1986 extended licensing authority to Federal laboratories and encouraged participation in Cooperative Research and Development Agreements (CRADAs) with the private sector.

Today, NIH has among the most active, effective technology transfer programs in government. Through this program, NIH has forged partnerships with industry, enhancing and augmenting the capacity of NIH to conduct laboratory and clinical research. For example, gene therapy research and the development of taxol as an anticancer agent have been greatly accelerated through CRADAs with the private sector.

Technology transfer promises to advance public health while contributing to our economic prosperity and global competitiveness. To achieve this, NIH must continue to build the organizational structure necessary to facilitate technology transfer for NIH-supported investigators, and to develop effective, well-articulated program policies and guidelines. This must include a shared responsibility on the part of awardee institutions to protect the public investment in NIH-supported research. Initiatives in technology transfer include:

- *NIH Participation in Commercial Research Partnerships*
- *Information Management to Facilitate Public Access*

NIH Participation in Commercial Research Partnerships

NIH funds 90 percent of basic biomedical research in the United States and is the engine of the biotechnology and pharmaceutical industries. Much of our success in translating basic discoveries to patient benefits has been due to the Technology Transfer Act of 1986 and the Bayh-Dole Act of 1980 , which encourage industrial linkages. Government-fostered collaborative relationships between NIH and industry define our technology transfer activities. These activities also give rise to new issues, not always anticipated, such as potential conflicts of interest, conflicts over Federal filing and holding of patents, and concerns about reasonable pricing of drugs developed with public monies. Another emerging issue involves the exclusive, proprietary control of licensing and commercialization of present and future NIH-funded research by domestic and foreign corporations.

Clearly articulated technology transfer policies and guidelines are central to preserving the integrity of the NIH community and its industrial partners. The policies under consideration include the development of consolidated guidelines covering real or potential conflicts of interest, revised material transfer agreements, and institute manuscript review procedures to identify inventions that could be patented. Formal policies also are under review and revision for CRADAs with small business and domestic corporations, and

SCIENTISTS AND STUDENTS USE COMPUTER TERMINALS AT THE NATIONAL LIBRARY OF MEDICINE TO ACCESS THE WORLD'S LARGEST BIOMEDICAL RESEARCH DATABASE.

clear, objective standards regarding such licensing provisions as fair and reasonable pricing of products licensed by NIH are being developed. NIH also is examining the collaborations between extramural researchers and the independent sector that have developed since 1980.

Issues have been raised about the appropriate role of NIH, in concert with other public and private institutions, in assuring that the public investment in biomedical research is reflected adequately in the prices of products brought to market as a result of joint NIH-private sector collaborations. In developing policy in this important area, NIH will continue to work closely with officials within DHHS, Congress, and with our research partners. In implementing a strong technology transfer policy, NIH recognizes our obligation to defend vigorously the intellectual property developed for the public with NIH resources. Without industrial partners, the NIH technology transfer mission cannot be executed in a successful manner. It is therefore imperative that NIH chart a steady and predictable course as it refines these policies.

INFORMATION MANAGEMENT TO FACILITATE PUBLIC ACCESS

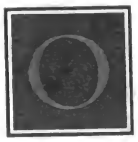
Technology transfer will be accelerated significantly by providing industry with timely information about the inventions of NIH-supported investigators available for licensing. Similarly, electronic information will keep scientists in government, industry, and academia informed about ongoing research to help promote greater collaboration.

Already, the NIH Office of Technology Transfer has developed a prototype electronic bulletin board to keep industry informed about intramural technology available for licensing. NIH is identifying the information needs of both industry and investigators in the private and public sectors, and evaluating sources of on-line information systems.

MAJOR GOALS: TECHNOLOGY TRANSFER

- *Work with DHHS, Congress, and research partners to establish and implement rational technology transfer policies.*
- *Establish timely and effective procedures and guidelines that will facilitate patenting, licensing, and cooperative research projects within intramural NIH.*
- *Encourage and provide incentives for NIH intramural scientists to participate in technology transfer through patenting.*
- *Establish a task force in the Office of the Director to review existing collaborative industrial relationships that have arisen at major NIH-funded research universities, and their history of patenting and licensing, to guide policy development and refinement with extramural NIH.*

NIH Leadership Base



UR STEWARDSHIP CAN BE NO BETTER THAN OUR STEWARDS. HUMAN INTELLECT IS THE MOST VALUABLE RESOURCE THE NATIONAL INSTITUTES OF HEALTH CAN TAP IN FULFILLING ITS MISSION TO ADVANCE THE HEALTH OF ALL AMERICANS. TO RENEW AND SUSTAIN THIS resource, NIH must establish and maintain a stable, nurturing environment that promotes creativity and innovation. Particularly critical is the ability to attract effective leaders in science and administration, to replenish the cadre of NIH leaders, and to sustain the talent and leadership needed to meet existing and emerging research challenges.

To address this critical issue, NIH will undertake three initiatives. First, a proposal will be developed for a comprehensive personnel system that will sustain and improve its capacity to recruit, retain, and reward top individuals. This system must recognize the marketplace in which it competes and be sufficiently flexible to address the special needs of a research institution.

Second, programs will be reviewed, and new ones will be initiated as needed, to identify aggressively and train future leaders for NIH. This will be a comprehensive leadership development program to select and provide training and job experiences to individuals who are expected to be placed in supervisory, managerial, and executive positions.

Finally, the agency will examine its recruitment procedures, particularly for senior and mid-level scientists, and develop an initiative to make them more effective. A trans-NIH recruitment and career development strategy will be crafted, and follow-up programs, such as orientation and mentoring, will be addressed.

In each of these initiatives, special emphasis will be placed on opportunities for women, minorities, and persons with disabilities.

Major Goals:
NIH Leadership Base

- *Develop a new personnel system tailored to NIH's need to recruit, retain, and reward employees in successful pursuit of its mission.*
- *Establish a Comprehensive Leadership Development Program to identify leaders and encourage their growth.*
- *Improve recruitment strategies, particularly those needed to successfully recruit and retain women, minority groups, and people with disabilities, and to increase employee appreciation for harmony and diversity in the workplace.*

Cost Management

Even as NIH's research opportunities continue to grow, increases in funding for biomedical research must compete with other sectors of the economy for finite resources. This means that many biomedical scientists will experience difficulties in bridging the gap between their research needs and the available research support. In this fiscal climate, prudent and effective cost management approaches must be implemented across all strategic priorities identified in this plan.

Decisions on the most appropriate approaches to management of resources, including human resources, must be informed by thoughtful and deliberative judgment. NIH recognizes that cost management principles must be even-handed, neither restricting funds necessary for the conduct of research nor reimbursing expenditures in excess of what is reasonable or affordable. These principles must be applied with equal rigor to both the direct and indirect components of the total costs of research.

The direct cost component should be managed throughout the granting process, beginning at the point at which proposed budgets are prepared by investigators and proceeding through the review process to the stage at which awards are made. Along this continuum it is possible to introduce cost management strategies that will assist NIH in arriving at an appropriate and affordable level of funding for each research project grant.

Core Principles for Funding of Research Project Grants

- The average cost of a cohort of competing grants will not exceed the average cost of the previous year's cohort by more than the Biomedical Research and Development Price Index.
- Noncompeting grants, on average, will not increase by more than 4 percent, excluding nonrecurring costs.
- Budgetary reductions will be achieved through a combination of peer review recommendations, staff review for cost allowability and reasonableness, and programmatic adjustments to arrive at an appropriate funding level.
- Award reductions of 25 percent or more below the initial peer review recommended level on a single grant application may require a revised statement of specific aims and a revised budget from the principal investigator, which must be reviewed and approved by program and grants management staff. For competing continuation (Type 2) grants, one factor in arriving at the award amount will be the level of support in prior years and the extent to which the institute can permit growth within the existing constraints on increases in average costs.
- The average length of research project grants will be four years.

The indirect cost component continues to come under scrutiny, aimed at maximizing accountability, standardization, and simplification, and providing incentives for cost savings. Particular attention must be given to the reimbursement for facilities costs. While this component has been increasing throughout the 1980s and 1990s, little is known about the extent of potential future costs. Studies must be undertaken to identify these costs in detail and to develop appropriate reimbursement strategies. Although indirect cost reimbursement policy is set by the Office of Management and Budget through its guidance circulars, NIH should participate in analysis and policy development, because NIH is the major payer of research overhead.

NIH will effect cost management strategies that reinforce a strong and rewarding relationship between research partners (sponsor and recipient), articulate the benefits to both parties, and promote effective administration that contributes to stewardship and productivity, stability and predictability. Ultimately, the goal of cost management is to maximize the return to this Nation on its investment in biomedical research.

Major Goals: Cost Management

- *Review the granting process systematically to determine the need for additional cost management measures, and develop those measures where appropriate.*
- *Explore the feasibility of providing incentives to reward research investigators and organizations for cost-efficient behavior.*
- *Develop and evaluate cost management tools and strategies, such as computer-simulated models, to project potential consequences of applying different cost management approaches.*
- *Participate with appropriate Federal agencies to study and develop reimbursement strategies for indirect costs, particularly the facilities component.*
- *Develop strategies that balance the relationship between the direct and indirect components of the total costs of research.*

Peer Review

THE INDEPENDENT PEER REVIEW SYSTEM HAS BEEN A KEY TO THE SUCCESS OF NIH. TO ENSURE THAT THE BEST SCIENCE IS FUNDED, NIH MUST CONTINUALLY REEVALUATE AND STRENGTHEN ITS PEER REVIEW SYSTEM. HOWEVER, SCIENTISTS HAVE RAISED QUESTIONS ABOUT THE system — that the process is slow and burdensome; that new, innovative, and creative ideas are undervalued; that areas of rapidly expanding science are not readily accommodated by the existing study section structure; and that cronyism or scientific conservatism may influence some review groups. These concerns must be addressed, or the vitality and integrity of peer review itself could be compromised.

Since 1946, NIH has employed a two-tiered peer review system to evaluate the thousands of grant applications it receives yearly. The first level of peer review is performed three times a year by more than 150 Initial Review Groups (IRGs) charged with the responsibility to assess grant applications for scientific and technical merit. In all, more than 2,400 individuals participate in peer review each year. IRG members are among the most knowledgeable, well-respected scientists in their fields, and are drawn broadly from the scientific community. Their assessments of each application are compiled in a summary statement that provides a critique of the proposed research, as well as a priority score and a percentile rank. In 1992 alone, these IRGs reviewed a total of 28,000 grant applications for research and training support, with some of the grant submissions several hundred pages in length.

As the scientific community has grown in numbers and science has grown in complexity, NIH peer review policies and procedures have been modified to meet changing conditions. In the process, NIH also has sought to meet the need for a growing number of scientists qualified to engage in peer review across all areas of biomedical and behavioral research. Since NIH peer review is a dynamic, not static, process, it will continue to introduce changes to improve its effectiveness and quality.

Initiatives in the area of peer review include:

- *Enhancement of Initial Review Groups*
- *Guidelines for Multi-Investigator Funding Mechanisms*
- *Improved Oversight of the NIH Review Process*

Enhancement of Initial Review Groups (IRGs)

The success of NIH extramural programs depends heavily on the quality of individuals who participate in the peer review process. Thus, NIH seeks to encourage the service of the most qualified scientists on Initial Review Groups and to broaden their overall level of participation. To achieve this, NIH must communicate information about the need for qualified reviewers and the importance of service on study sections to a wider segment of the scientific community, as well as to senior staff of the institutes. Scientists who participate in peer review must be prepared to make objective decisions regarding the merit of a research project, free of any conflicts of interest, and equipped with the expertise necessary to review specific grant applications.

Specific recommendations to ensure the highest quality peer review include the following: (l) conducting periodic evaluation of the process by which the institutes suggest members for the IRGs; (2) holding periodic meetings with NIH leadership and chairpersons of IRGs to exchange views and evaluate peer review policies and procedures; and (3) developing a comprehensive communications package of videotapes, hand-

books, and other materials to inform and educate all scientists who become members of the IRGs.

Guidelines for Multi-Investigator Funding Mechanisms

Many institutions across the country receive program project and center grants awarded to principal investigators involved in broad-based, multidisciplinary, multiyear research ranging from basic science to clinical projects. To ensure fairness and objectivity, NIH seeks to develop well-defined guidelines for program project grants involving multiple investigators. Currently, the review procedures and practices for program grant applications differ among institutes. To ensure equity of opportunity among applicants, NIH will closely examine and refine these procedures to ensure their uniformity across NIH. Regular review of the program needs of institutes whose missions are advanced by these interdisciplinary research projects will also go a long way towards ensuring that projects of greatest scientific merit are funded.

Improved Oversight of the NIH Peer Review Process

The peer review process traditionally has been overseen primarily by staff of NIH. Yet the changing nature and increasing complexity of biomedical research has made this task increasingly difficult. More than ever, these administrators need up-to-date knowledge of emerging trends and fields of scientific research in order to make the critical scientific judgments necessary to fine tune the peer review process.

One result is that the biomedical sciences are now divided among many IRGs. On the one hand, some review groups are too narrow in scope, with undue emphasis on a particular subspecialty or biological method. In other cases, there may be no chartered review group to cover a new, emerging field.

To address these problems, NIH will spearhead a reorganization of the oversight of its peer review process, with particular emphasis on (1) assigning IRG grant applications in a reasonably broad subject area of science that has been determined to be of long-term significance to the mission of NIH, (2) conducting regular evaluations of the need for existing IRGs, (3) establishing new review panels with expertise that includes a variety of approaches germane to particular biological fields, and (4) achieving greater uniformity of review practices by advisory councils and boards.

Major Goals: Peer Review

- *Establish a central NIH Advisory Group that includes extramural scientists to oversee the structure and procedures of the overall peer review system, including the disciplinary function and distribution of IRGs (i.e., study sections) and the review procedures of councils and boards.*
- *Sustain and enhance the quality of peer review with an emphasis on identifying innovative aspects of grant applications.*
- *Develop means to increase the willingness of highly qualified scientists, including women and members of minority groups, to serve on IRGs.*
- *Develop means for assuring the quality and uniformity of peer review being conducted by individual institutes outside of the Division of Research Grants.*

Public Trust

Always do the right thing, it will gratify some people and astonish the rest.

— *Mark Twain, American author*

s a public enterprise of vital importance to every man, woman, and child in this country, we must hold ourselves to the highest standard. Only by so doing will we continue to deserve the public's trust. In opinion polls, NIH consistently ranks among the most respected government agencies, but this respect cannot be taken for granted. The rapid progress and growing complexity of science and the public's heightened expectations for the research enterprise necessitate closer attention to social, legal, and ethical issues inherent in biomedical and behavioral research; professional standards of science; efficient communication of facts to the public; the impact of research on health care, and transferring technology and fostering collaborative endeavors in the public interest.

Biomedical research pursues the universally accepted goals of improving health and reducing the burdens of disease and disability. Progress in the pursuit of those goals can occasionally present difficult social, legal, ethical, and economic challenges. Increasingly, the scientific community and the public and its representatives are confronted with complex questions concerning the content and conduct of research and the application of discoveries and innovations to health needs.

For example, clinical research on women of child-bearing age, children, the elderly, the indigent, and minorities raises a host of ethical issues and safety concerns, ranging from potential health risks to obtaining informed assent and consent from vulnerable subjects. Other sensitive issues include research on pathological behaviors, such as violence; research involving human fetal tissue; and compassionate use of experimental therapies. In the area of human genome research, there is a great need for guidance and new policy constructs on ethical, legal, and social issues. As new genetic knowledge and subsequent therapeutic modalities present opportunities for revolutionary improvements in health care, they also raise the potential for inappropriate or unethical use of this knowledge, such as abuse of privacy, discrimination in employment or education, and restricted access to insurance.

A growing number of science policy issues increasingly compete for the attention of society, policymakers, and the biomedical research community. If these issues are not addressed responsibly and comprehensively, they could undermine public trust in science and its institutions. This could impede research and delay public acceptance of the fruits of discovery.

NIH will carry out its leadership responsibility to identify, prioritize, and analyze social, legal, ethical, economic, and associated issues that arise from NIH-supported research. To address these concerns both comprehensively and expeditiously, NIH will put in place a formal system for addressing these issues, with the aim of seeking broad public input and developing policy recommendations. The major NIH initiative in this area is:

- *Science Policy Studies Center*

Science Policy Studies Center

The new NIH Science Policy Studies Center, established in January 1993, will provide a centralized capability to address, in a forward-looking, systematic manner, cross-cutting science policy issues that affect the entire NIH research enterprise and the agency's ability to carry out its mission. Through studies and development of policy options and recommendations, the Center will help inform science policy decisionmaking. Center-developed policy recommendations will help ensure that NIH-supported research continues to be conducted in an ethically and socially responsible manner.

NIH will also consult with outside individuals and organizations as it addresses social, legal, ethical, economic, and associated issues that bear on the performance of biomedical research and its role within society. Through its new Center, NIH will forge working partnerships with individuals and organizations with expertise in the many areas that pertain to NIH's science and health mandates. Such cooperation will ensure balanced evaluations of complex, often controversial issues.

Major Goals:
Social, Legal, Ethical, and Economic Issues in Biomedical Research

- *Implement the NIH Science Policy Studies Center and integrate the policy options and recommendations developed through its studies into NIH's decisionmaking process, doing so with broad input from affected communities.*
- *Establish a Scholars Program to attract prominent individuals to work within the NIH Science Policy Studies Center for a limited time.*
- *Develop an "early alert" capability within the Center to track and evaluate medical innovations and scientific advances to permit early identification of potential social, legal, ethical, and economic issues arising from NIH-supported research.*
- *Enhance the research community's understanding of and sensitivity to the importance of addressing social, legal, ethical, and economic issues during the early phases of research.*

NIH and the Nation's Economy

NIH-supported research contributes significantly to the Nation's economic prosperity, and the size of those contributions continues to increase. Translated into new or improved prevention, diagnostic, and therapeutic technologies, scientific understanding of health and disease has reduced the costs associated with injury and illness. According to a 1990 analysis, for example, 26 technologies derived from research supported by an NIH investment of about $800 million, yield annual cost savings exceeding $6 billion, translating into a 600 to 800 percent annual return on investment.

The health of U.S. citizens underpins the Nation's productivity. Conversely, soaring expenditures for health care undermine efforts to improve U.S. productivity and industrial competitiveness. Knowledge and methods generated by biomedical research are critical to efforts to improve the health of the U.S. workforce, reduce worker absenteeism due to poor health, and to rein in health-care costs that now represent over 13 percent of the gross domestic product and account for nearly 12 percent of Federal expenditures. The spiraling cost of health care is one of this Nation's most vexing problems, and NIH must be part of the solution. Effectively applied and widely disseminated, information and tools generated by NIH-supported research will help control costs in the long run. The challenge is to translate research results into useful applications and speed the transfer of these applications to the appropriate target populations, such as physicians, hospitals, public health departments, schools, or neighborhood clinics.

NIH-sponsored research also generates knowledge, ideas, and technology that important U.S. industries have converted into competitive advantages. NIH's sustained support of basic biological research launched the U.S. biotechnology industry to its world-leadership position. The much larger U.S. pharmaceutical industry, also an international leader, has benefited enormously from the NIH-supported infrastructure for research and training.

The links between NIH's mission to improve human health and the Nation's economic well-being are many, if not always well recognized by members of the public and their representatives. NIH is strengthening these links with the aim of reducing the social and economic burdens of disease and disability, and consequently reducing health care costs. In parallel, it must evaluate and communicate the full impact of its research to help guide budgetary decisions that affect the scope and direction of NIH's research programs. An initiative in this area is:

- *Economic Impact Studies*

Economic Impact Studies

NIH, under the auspices of the NIH Science Policy Studies Center, will regularly conduct analyses of the social and economic costs of specific diseases and the impact of NIH research on reducing these costs. Continuing analysis of the burdens of illness — extending beyond morbidity and mortality to include associated spending for health and other costs — will help NIH set its research priorities and target activities within those priorities.

The results of such studies also will help NIH demonstrate and communicate the tangible benefits that can be traced to biomedical research. In addition, the information will be especially useful to the NIH leadership not only in developing its budget request but in justifying that request before Congress. Reliable impact analyses could also lengthen planning and budgeting horizons by demonstrating the benefits that can accrue to long-term basic research efforts.

Major Goals: NIH and the Nation's Economy

- *Initiate economic impact studies to determine cost implications and changes in health and health care practices and delivery as a result of NIH research and outreach efforts.*
- *Identify and analyze major current and emerging economic issues arising from NIH-supported research, and develop options for policy recommendations as needed.*

THE COMMUNICATION OF SCIENTIFIC AND HEALTH INFORMATION IS ESSENTIAL TO NIH'S MISSION. APPLYING THE KNOWLEDGE GENERATED BY NIH RESEARCH TO EXTEND HEALTHY LIFE AND REDUCE THE BURDENS OF ILLNESS AND DISABILITY REQUIRES OPTIMAL COMMUNICATIONS. It is crucial that NIH communicate effectively with many groups: scientists engaged in biomedical research; health care practitioners of all types; patients; members of the general public; the media; and the Congress.

NIH must strive to ensure that biomedical research as well as health policy, health practices, and health news coverage are based on the best scientific information available. New advances critical to health must be communicated accurately and expeditiously. It is also important that the NIH be seen as a credible, accessible resource for information. Well-designed programs of information and outreach contribute to the perception of NIH as a valuable public resource.

Regional meetings on the Strategic Plan have underlined the fact that NIH needs to put more emphasis on communicating with the general public on a more local basis. The substance of NIH's communications programs should include information on the latest research advances and consumer-oriented health messages, but should also convey the creative process of science.

An enhanced communications program will provide valuable information on health choices, inspire young people to enter careers in the life sciences, and elevate the scientific literacy of the general public. Enhanced communication will benefit NIH: without the support of the public, NIH cannot thrive. The major initiative in this area is:

- *Trans-NIH Communications Strategy*

TRANS-NIH COMMUNICATIONS STRATEGY

A trans-NIH communications strategy will be developed to ensure optimal use of the communications components throughout the institutes. The plan will coordinate health messages and information on new scientific discoveries through better integration of NIH resources and enhanced reliance on computer and video technology.. Special emphasis will be given to coordination with grantee institutions, regional health organizations, and existing health networks to ensure broad dissemination of the results of publicly funded research. The trans-NIH communications strategy will enlist wider use of new communications technologies.

MAJOR GOALS: COMMUNICATING WITH THE PUBLIC

- *Develop over the next year a coordinated trans-NIH communications strategy that includes NIH grantee institutions and state health departments in the NIH Public Outreach Network.*
- *Target increased coverage of NIH across the Nation, emphasizing mid-sized city media markets and background programs for regional reporters.*
- *Improve access to current research updates for patients and for health care professionals, particularly those in underserved rural and inner-city communities.*

A Special Word of Thanks

The development of this Strategic Plan for the National Institutes of Health was assisted by the more than 2,000 scientists, physicians, policy makers, government officials, and others who contributed so generously of their time, energy, expertise, and critical review. To them, we pay special tribute and thanks.

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